# THE ENDOCRINES IN GENERAL MEDICINE

W. LANGDON BROWN
M.D., F.R.C.P.

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MODERN MEDICAL MONOGRAPHS

Edited by

HUGH MACLEAN, M.D., D.Sc., F.R.C.P.

*Professor of Medicine, University of London*

# THE ENDOCRINES IN GENERAL MEDICINE

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BY

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# PREFACE

In this book I have attempted to give a brief account of the endocrine system and its diseases in a form which I hope may be of service to the general practitioner. I have tried to view the system as a whole and not merely as a number of isolated units. One drawback of the method is that it involves some degree of repetition.

There are several encyclopædic works on the subject, full of detail, which, however valuable to the special worker and for purposes of reference, are on too large a scale for the busy practitioner to assimilate. There are also books dealing purely with the physiology of the ductless glands, necessarily cautious in tone, which are perhaps apt to leave the impression that clinical methods are of little avail in unravelling the problem. There are others which are more frankly speculative.

This book is chiefly a record of my own personal experience, first in the laboratory, later at the bed-side. I have tried to link the physiological and clinical methods, and to give an account of the biological position of the endocrine system in relation to the visceral nervous system, which seems to me to provide a key to its mode of action.

Some of the material has already appeared, though in a different form, in various articles in the *British Medical Journal*, the *Clinical Journal*, the *British Journal of Psychology*, the *Medical World*, and the *New York Medical Journal*. I am indebted to the Editors of these journals for permission to make use of such material.

I am also indebted to my House Physician, Dr. H. L. Wilson, for kindly reading the proofs, and for several useful suggestions.

W. LANGDON BROWN.

81, Cavendish Square, W.1.
*March 17th*, 1927.

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# THE ENDOCRINES IN GENERAL MEDICINE

## CHAPTER I

## THE BIOLOGY OF THE ENDOCRINE SYSTEM

Few subjects in medicine have so powerfully stimulated interest and imagination of recent years as endocrinology. It provides the missing link between biology and psychology, and has profoundly modified our conception of disease. But the theory of internal secretion has always been in advance of the facts. The very name was introduced by Claude Bernard when the only known example was the glycogenic function of the liver. Brown-Sequard's interesting hypotheses of internal secretion rested on but a small substratum of fact. Yet subsequent observations have confirmed many of their generalisations. This may happen with some of the speculations on endocrinology which are rife to-day. But we must remember that it has not yet occurred.

To a certain extent every product of cell activity has an effect on every other tissue. The more widely tissues differ, the more they can make use of the end-products of the other's metabolism. Thus, while animals ultimately depend on vegetables for their food, the carbon dioxide excreted by animals is actually a food for plants, and their urea is an important source of nitrogen to them. For animals themselves such substances are merely stimulant in the sense that they contribute to the process of their own removal. Thus carbon dioxide is a respiratory stimulant and in small doses actually improves the contraction of the heart. By this action on respiration and circulation its excretion is facilitated. Similarly

urea is a diuretic, which is an obvious advantage. But neither carbon dioxide nor urea can act as a food for animals, or quicken their vital processes in any other way. It is true that an intermediate product of metabolism, creatine, which is produced by muscles, is a stimulant to gastric secretion, and increases the rate of growth. It is also true that in starvation the autolytic products of all the cells are pooled, and the various organs nourished from this common stock in proportion to their relative importance. But it may be asserted, in general terms, that the more similar tissues are, the less can the one make use of the other's end products of metabolism. A specially elaborated secretion is required to produce a beneficial action. Of such secretions the hormones produced by ductless and other glands are outstanding examples. The term "hormone" (*ὁρμάω* "I excite") was introduced by Starling on Hardy's suggestion. They appear to be bodies of comparatively small molecular weight: unlike ferments, they are not destroyed by simple boiling, but are rapidly destroyed by oxidising agents. They are decomposed in the tissues they excite, and do not escape in any of the excretions.

Another thing which we can learn from comparing animal and vegetable bio-chemistry is the powerful effect of even infinitesimal doses. The importance of vitamins is now clearly recognised. Vitamins are as characteristic of vegetable as are hormones of animal life. They have been termed exogenous hormones; chemically vitamins and hormones are not greatly dissimilar, while both are intensely effective in minute doses. The deficiency diseases, following lack of vitamins, illustrate once more the dependence of animal upon plant life. Moreover, McCarrison has shown that vitamin defects lead to endocrine changes; the adrenals and pituitary enlarge, while other endocrine glands show more or less atrophy, indicating some close relationship between hormones and vitamins.

### THE ORIGIN OF THE ENDOCRINE GLANDS.

Julian Huxley, in his illuminating and suggestive *Essays in Popular Science* (Chatto & Windus, 1926),

points out that there are three stages in the development of the ovum after fertilisation. The first is a simple physical process of dividing the egg into cells of convenient size; its course can be disarranged within wide limits without altering normal development. The second is one of chemical differentiation. In a position determined by the point of entrance of the sperm an "organising area" appears, which brings about irreversible changes in the tissues with which it is contiguous, the effect radiating outwards along certain gradients. The third stage is one of functional differentiation. The most fundamental of these is the chemical stage. Some chemical differentiators are short-lived, such as that formed in the tadpole's gills, which dissolves the gill covers when the time comes for the limbs to develop. Essentially the hormones would appear to be persistent survivals of such chemical differentiators; in fact, specialisations of the chemical stimuli to which animals reacted before there was a nervous system at all. They reveal their antiquity in the way they cling to vestigial structures. On Gaskell's theory of the origin of the vertebrates most of the endocrine glands will be found to represent modified nephridia, which were previously segmental and paired. McCallum regards the earliest function of nephridia not so much the elimination of waste products as the regulation of the inorganic composition of the blood. It would appear that, just as certain groups of nephridia are condensed into kidneys, which keep the composition of the blood constant by subtraction, certain others, which have had their original outlets dammed up by the formation of new structures, secrete into the blood, keeping its composition constant by addition.

Comparative morphology points to the conclusion that the most anterior groups of nephridia are condensed into a gland which becomes the pituitary, while in the neighbourhood of the gill-slits segmentally arranged structures give rise to the tonsils, thyroid, parathyroids, and thymus, in the position which might be expected if they are homologous with the second group of nephridia. It will be noted that two of these are now lymphatic in structure, while the others are glandular. Now in both

the invertebrates and the lower vertebrates part of a nephric tubule may become converted into lymphoid tissue, which shows its association with excretory functions by taking up injected alizarin blue and carmine into its leucocytes. A nephridium may thus differentiate in two directions. But it may become modified in yet a third direction. The position and arrangement of the uterus in Limulus or King Crab closely resembles that of the thyroid with its thyroglossal duct in the most primitive vertebrates, explaining "the relationship which has been known from time immemorial to exist between the thyroid and the sexual organs" (Gaskell). Further down the body in the Elasmobranch fishes, closely connected with the kidneys, are the interrenal glands, which are probably pronephric in origin, and which were shown by Swale Vincent to represent the adrenal cortex.

Circumstances alter function. Not infrequently, therefore, when in the course of evolution a structure has become useless for its original purpose, the endocrine system provides it with a new tenant. It reminds one of the hermit crab, that seizes on an empty whelk shell. And just as the hermit crab existed before it found an empty house, so the endocrine functions were in existence in a less specialized form before they had a local habitation. The pineal body, however, differs from the structures already described in being not a modified nephridium, but the remains of a median eye. Although it illustrates a change of function, it is doubtful whether it should be classed as an endocrine structure at all. Llewellys Barker considers that it exerts its effect through the basal ganglia rather than by a direct secretory action.

### TROPISMS AND INSTINCTS.

Internal secretions further reveal their antiquity in the way that they regulate instinctive behaviour. Before a nervous system was developed at all, and even later when, although constituted, it had not yet acquired the elaborate associative mechanisms present in higher vertebrates, animal responses chiefly took the form of heliotropism, chemiotropism, geotropism, stereotropism, and the like.

It might appear that an animal so directed would act like an uncontrolled machine and soon meet with disaster. That this may readily happen is sufficiently illustrated by the behaviour of a moth towards a candle. That it does not invariably happen is due to internal controls apparently of a chemical nature. Thus, Loeb has shown us that bees before the nuptial flight become intensely positively heliotropic, but immediately afterwards the Queen Bee loses this heliotropism and becomes stereotropic, which leads her to begin a subterranean existence where the new nest is founded. The condition of the gonads here profoundly modifies the tropism of the animal. Animals that are indifferent to light can be made positively or negatively heliotropic by certain chemical substances such as acids, alcohol and caffeine. Thus Daphnia become positively heliotropic in the presence of $CO_2$. A caterpillar acquires a positive heliotropism until it is well-fed, when it loses it; in this way it finds the few young leaves at the top of a twig towards which it is driven by its heliotropism; having eaten these, it is free to move down again until again driven up another twig by the same process. These simple examples show how the conduct of an animal without associative mechanisms (and therefore without consciousness as ordinarily understood) is modified by chemical means. As Loeb says, the theory of tropisms is at the same time the theory of instincts, if due consideration is given to the rôle of hormones in producing certain tropisms and suppressing others.

### THE HORMONES IN FŒTAL LIFE.

From the nature of the case, the actual demonstration of endocrine activity in fœtal life is easier in the frog than in the mammal. Thus the secretion of the thyroid was shown by Gudernatsch to be the chief agent in the transformation of the tadpole into the frog. It is interesting to note that, if extraneous thyroid is given, the animal's own gland remains much underdeveloped; evidently the stimulus of having to provide secretion is one of the conditions required for full development of the gland. This suggests the need of caution in

organotherapy in children who have no endocrine deficiency.

But in the human fœtus active hormones have also been demonstrated. (Keene and Hewer, *Lancet*, 1924, Vol. 11, p. 111). Thus the pituitary gland yields an active secretion 8 weeks, the thyroid 11 weeks, the parathyroid 20 weeks, and the adrenal 16 weeks after conception.

Bolk has developed in an interesting, if somewhat speculative, manner, Loeb's conception of hormones exercising a selective repression in some directions so as to promote higher developments in others. Thus fœtal apes lack pigment and hair, and he attributes the partial persistence in man of such embryonic characteristics to a suppressive action of the adrenals. Again, he thinks that the human cranial sutures are kept open by the action of the thymus, thus allowing the brain to reach its present eminence. He attributes the existing conformation of the human skull to the pituitary, so that when this is diseased, as in acromegaly, there is a reversion to a simian shape. One might add that the changes in osteitis deformans could be similarly explained. He regards the pineal gland as retarding sexual maturity, in the interests of a more prolonged somatic development, for in higher species the individual counts for more and fertility for less. In anencephaly the growth of the brain stops at the fish stage, while the adrenal cortex fails to develop in the striking way it does when the cerebral hemispheres grow normally. Elliot Smith suggests that more probably the great development of the brain is directly responsible for repressing simian traits, the endocrine glands being at most the mechanism through which this works. This would be more in accordance with the general trend of evolution. For, as he says, man has become the greatest of the primates because of his faithful dependence upon the development of the brain. But in this connection between the development of the central nervous system and the adrenals I would suggest that we may come to find the explanation of the somewhat similar symptoms produced by cortical adrenal tumours and diseases of the pineal body.

Keith (Herter Lectures—*Johns Hopkins Hospital*

*Bulletin*, 1922, No. 375, p. 155, No. 376, p. 195. Huxley Lecture—*Nature*, 1923, Vol. 112, pp. 257–268) takes an even wider view in postulating that the hormones provide a mechanism which co-ordinates the development and growth of the diverse hordes of embryonic cells and produces a harmonious result. He points out the important fact that human characters first arose in the anthropoid womb; the long intra-uterine existence of the mammals, especially the higher primates, gives the endocrine system the shelter necessary for the working out of its experiments. Whether these experiments establish themselves or not will depend on natural selection. Many constant structural modifications of man's body, *e.g.*, the arrangement of the spinal muscles, are first seen as occasional variations in the body of the ape. Similarly, characteristics which are merely fœtal in the ape become persistent in man, such as the cranial bend in the front part of the base of the skull. In the chimpanzee at the 7th month the hair is distributed exactly as in a baby at birth, and at a still earlier stage its skin is almost free from pigment. Further, he believes that hormonic influences determine racial differences, the pituitary in the European, the thyroid in the Mongol, and the adrenal in the Negro. In the last two instances I would suggest that it is defect rather than predominance of the hormone which seems responsible. Crookshank in his interesting book, *The Mongol in our Midst*, is so impressed with the similarity between the hormonic types of orang and Mongol, chimpanzee and European, gorilla and Negro respectively, as to adopt a polygenetic origin for man, each of these races springing from the corresponding anthropoid; but this view presents anthropological difficulties, and Keith thinks that the Mongol and orang are only superficially alike because they have inherited a common mechanism of growth hormones.

J. T. Cunningham in his book, *Hormones and Heredity*, suggested that hormones could influence the germ plasm, but Keith considers that, as far as possible, nature seems to have safeguarded the progeny by isolating the gonads from the functional influences of the parental body. He agrees, however, that the germ plasm can be injured by

toxic substances from without. Even to hint at the possibility of the inheritance of acquired characters is rank heresy to-day, and I am not going to hazard excommunication. I would merely point out that the emotional nervous system, as I shall show presently, is in close association with the endocrine system, which in turn co-operates with the gonads. The germ plasm of the two sexes has, prior to fertilisation, to extrude some of its nuclear substance. The great advantage of this is that, on fertilisation, there is a recombination of the genes ; thus favourable mutations can arise which facilitate evolutionary change. At present we are ignorant of the factors determining which portion is extruded. Whether the discard is from a strong or weak suit, so to speak, must undoubtedly influence the make up of the offspring. It does not seem beyond the bounds of possibility that the autonomic nervous system acting through the endocrine glands may play a part in determining the discard. But it must be admitted that many apparent Lamarckian adaptations are not inherited, but are acquired afresh in every generation through the everyday activities of the individual.

### THE ENDOCRINES AND THE VISCERAL NERVOUS SYSTEM.

Bayliss and Starling's discovery of secretin in 1902 opened out the vista of a chemical control of the body in which the nervous system merely acted as a trigger, firing off a series of reactions. This conception was elaborated until it bid fair to dethrone the nervous system from its supreme position, although Langley's generalisation that the action of adrenalin on any part is the same as that obtained by stimulating the sympathetic should have suggested otherwise. For, considering the struggle the nervous system has had to obtain control, it was not likely to abdicate its suzerainty in favour of the more ancient dynasty of chemo-tropism.

We ordinarily think of the evolution of the nervous system as peacefully accomplished. A struggle for supremacy between two animals or two species we recognise. But it would appear that a similar struggle accompanies the integration of the multicellular

individual. Many apparently peaceful events in nature prove on closer analysis to involve a concealed struggle. Man is a gregarious animal, but he has not found it an easy task to adjust the desires of the individual to the needs of the community. Philosophers may lament this, theologians may attribute it to original sin, but it should lead the biologist to enquire whether the cells of which he is composed have always found it easy to sink their individuality in that of the organism. The thesis of a hostile symbiosis between the tissues of the body has been skilfully upheld by Morley Roberts. (*Warfare in the Human Body*, Eveleigh Nash & Grayson.) A strong central government is needed to keep order, and no high degree of differentiation is possible in the animal body without the control of a centralised nervous system, which has gradually acquired an increasing predominance. It is not too much to say that this control, though for the benefit of the body as a whole, may be resented by the individual tissues. Wilfrid Trotter* has developed the argument of an hostility between nervous and somatic tissues, which is expressed in the way the former insulates itself.

Without defensive mechanisms no animal can survive in the struggle for existence, and no method of defence remains impenetrable, for, if it were, the species possessing it would multiply to the exclusion of others. As evolution proceeds the apparatus for defence comes under the control of a central nervous system.

A central nervous system enables very rapid reactions to occur, and the need for such rapidity of response will first be experienced in the struggle for existence, when its advantage is at once manifest. A nervous system starts as a series of independent receptors and effectors in the deeper layers of the skin, the cells of which sink in deeper and deeper, until they become concentrated into a central nervous system. Between the receptor and effector an adjustor mechanism develops, which is the germ of the whole associative apparatus. It is not too fanciful to compare the origin of the nervous system to a group of settlers on the coast, who gradually invade the interior,

* Horsley Lecture—British Medical Association, 1926.

first singly and then in an organised army, as in the nervous system of vertebrates which arises as a tubular invagination from the surface. Once established, the invader assumes control over the indigenous inhabitants, fortifying itself as it goes, and maintaining its protectorate by a system of rapid communication throughout the invaded areas. The biological and sociological parallel is remarkably complete.

Now a wise military occupation utilises existing institutions, and the lowest level of the nervous system, which is the autonomic or vegetative portion, enters into a close association with the older chemical methods of control. Thus we have, hand in hand, an increasing concentration of the government in the central nervous system and an increasing concentration of endocrine functions in glands which can no longer discharge their primitive functions. The autonomic or vegetative level of the nervous system consists of two great divisions, whose relation to the endocrine system may be summarised thus :—

(1) **Parasympathetic or Extended Vagus.** This is anabolic, storing potential energy. It therefore co-operates with the digestive system, which obtains energy for the body from the food ; and diminishes the amount of sugar in the blood, storing it in the tissues. The cell-islets of the pancreas and the parathyroids are clearly anabolic in function, and direct vagus control over the former has recently been proved. (G. A. Clark, *Journal of Physiology*, 1925, Vol. LIX, p. 466.)

(2) **Sympathetic.** This is katabolic, producing kinetic energy. It co-operates with the adrenals, thyroid and pituitary. It also raises the amount of sugar in the blood to provide energy for defence against (*a*) the external foe by flight or fight ; (*b*) the internal foe of bacterial invasion by pyrexia.

When these two divisions are distributed to the same structure their action is always antagonistic ; when one is stimulated the other is inhibited. The rhythm of life largely depends on the fluctuating balance between these two. The parasympathetic plays the chief part in the digestion and assimilation of food, the sympathetic spends the energy thus derived. In sleep the para-

sympathetic gains control, and the arrest of external manifestation of energy lasts until the balance is restored in favour of the sympathetic, when the subject awakens, ready to expend energy again. These different characteristics of the groups are reflected in the endocrine glands associated with them. Evidence is steadily accumulating as to the way in which the katabolic groups of glands mutually co-operate, while each antagonises the pancreas. Examples will be given in the appropriate place.

Activation for emotional response, then, belongs to the sympathetic group. We find that the gonads chiefly co-operate with this group, as might be expected from the large part sex plays in emotional life. In this way a basic tripod of sympathetic nervous system, katabolic endocrines and gonads came to be formed, to which were entrusted both the preservation of the individual and the continuity of the species. Their structural association is indicated by such facts as the common origin of the adrenal cortex and the interstitial cells of the gonads from the Wolffian body, and the development of the thyroid from the uterus of the arthropod ancestor. Their close association is shown in disease as well as in health, and is reflected in many psychoneuroses. Disease is not likely to manifest itself for long in one limb of this tripod without affecting all three.

From this summary account of the biological position of the endocrine system we may draw the following conclusions: (1) Endocrine glands are modified nephridia. To this rule the only exceptions are the medulla of the adrenals, the cell-islets of the pancreas, and the doubtful instance of the pineal.

(2) Endocrine functions are the specialisation of the old chemical methods of stimulation and defence that have become concentrated in structures which perforce had to change their functions.

(3) These chemical methods have gradually come largely under the control of the autonomic nervous system, which correlates them and enables them to be brought rapidly into action either for the ordinary processes of metabolism or for external and internal defence.

(4) The adrenals, thyroid and pituitary, are predomin-

antly katabolic, and co-operate with the sympathetic division of the autonomic nervous system. They also co-operate with the gonads.

(5) The pancreatic cell-islets and the parathyroids are predominantly anabolic, as is the parasympathetic division of the autonomic nervous system.

(6) The endocrine system plays an important part in instinctive behaviour and emotional life, as well as in determining growth and evolution.

## CHAPTER II

# THE ENDOCRINE SYSTEM IN CHILDHOOD

The energy derived from the reconstitution of the nucleus when the ovum is fertilised is, in effect, the driving force which carries man through his allotted span of years. It displays itself at once by rapid cellular subdivision and differentiation. Groups of tissues are thus formed, each striving to obtain the best conditions for itself and inevitably producing reactions in other groups. The position in fact recalls that obtaining in a building—a thrust in this direction or a strain in that is met by other structures, so that an illusory appearance of rest is given, when really it is merely action and reaction that are equal and opposite. Relentless pressure may, as in St. Paul's, reduce rubble to powder and then movement asserts itself; the dome begins to sink and to thrust its supporting piers outwards. So in the body an organ inferiority will determine its physical and even its mental posture. These internal stresses and strains are harmonised by two main agents—the control of the central nervous system, and those internal regulators, the endocrine glands.

We have seen that these glands begin to assert themselves early in fœtal life. As they can have no function in respect of external relation during this time, their secretions must be entirely occupied with internal regulation. So that from the first an endocrine defect must disturb the balance.

As the fertility of a species diminishes, the survival value of the individual increases. A fish may cast two million eggs into the water to take their chance; the offspring of less fertile animals call for maternal care. As the individual comes to require a longer prenatal development, pregnancy and parturition throw a greater strain upon the mother, so paternal care is also needed. An

increase in the time required for the offspring to attain adult existence makes still further demand on parental care. Thus retardation of development becomes possible in the interest of the individual. It is clear that intra-uterine life, while facilitating growth, delays completion of structure. Thus an infant born prematurely at the 7th month and dying at the time it should have been born shows greater medullation of the nervous system than a child stillborn at full term. But retardation is still maintained after birth by the pineal and the thymus. It may be urged that neither of these belong strictly to the endocrine system, because no active internal secretion has been found to be produced by them. With regard to the pineal I think this objection probably holds, because, as already pointed out, it belongs to an entirely different system to the others—it is a vestigial eye instead of a nephridium. It would appear to exercise its inhibitory effect directly through the central nervous system rather than by chemical means. With regard to the thymus, its structure does not suggest that it forms a secretion. It may, however, act in some other way. The involution of the thymus at about 7 appears to be accompanied by a partial involution of lymphatic tissue throughout the body, which is reflected in the blood picture. I do not think we have exhausted the possibilities of this system. We must admit we do not know how the thymus acts, but it is clear from animal experiments that its removal hastens maturity and that castration results in its persistence. Similarly, disease of the pineal is associated with premature sexual development. I would claim, therefore, that these two structures, one acting through the central nervous system, the other through the hæmopoietic system, definitely delay maturity in the interests of the somatic growth of the individual. Particularly do they delay sexual maturity—that is, they delay the diversion of energy to the needs of the next generation, while claiming longer attention from the previous generation.

During these years the adrenal cortex also seems to lie dormant: if it is thrown into activity by the formation of a tumour in its substance there is premature sexual development and precocious growth, of the type to which

the name "Infant Hercules" has been given. This is not to say that the adrenal cortex does nothing before puberty, for we have seen that there is some subtle association between completion of adrenal structure and the development of the brain.

The activities of the thyroid and pituitary express themselves differently in childhood and in adult life. In the child they are principally concerned with growth—the cretin is always undersized, so is the youthful "Fröhlich," or, as it is then sometimes called, the Brissaud type of infantilism. Overactivity of the anterior lobe of the pituitary, on the other hand, leads to gigantism, and in some curious way this may affect only one half of the body, producing hemihypertrophy. Defective action of the posterior lobe may result in diabetes insipidus in the child and adult alike. With the onset of puberty both thyroid and pituitary become closely associated with gonadal development. In my experience delayed gonadal development results in a pituitary type of obesity, which may be temporary. In other words, an apparently normal child becomes an abnormal juvenile, but may become a normal adolescent. For the continued activity of the pituitary, stimulation from the gonads is necessary, and the converse holds as well. But that the gonadal defect is sometimes primary I became convinced when I had some years ago in my out-patient department at the same time five cases of gross gonadal defect, either congenital or resulting from disease, which presented signs of hypopituitarism. The child showing such signs will have a retarded puberty at any rate. It is interesting to note that, if one or both upper lateral incisors be small, twisted, or displaced in a child, the establishment of puberty will probably be delayed or incomplete.

### INFANTILISM.

For some observers infantilism means some kind of endocrine deficiency, but it is clear that this is by no means always present. Falta has given a useful caution in pointing out that "if true infantilism comes about through the standing still of the whole organism at a juvenile stage, the endocrine system remains just as

childish as the rest." He takes these as the stigmata of infantilism—delay in the development of the gonads and secondary sexual characteristics, in the involution of the lymphatic apparatus, in ossification and in the union of the epiphyses, and in the development of the adult proportions. (It has been stated that the upper and lower lengths of the body as measured from the symphysis should become equal by the age of 25. Before this the lower length is the shorter ; though only slightly so after 15.) The pelvis is neither masculine nor feminine in type ; the psyche remains at the childish stage. Now this condition can arise from many causes which have nothing to do with the endocrine system. Any chronic disease in early life which interferes sufficiently with the vital processes may do it—such as congenital heart disease, extensive fibrosis of the lung and bronchiectasis, renal disease, pancreatic insufficiency in which the islets need not share, intestinal conditions and congenital œsophageal stricture. Then, again, toxins affecting the germ-cells, such as alcohol or syphilis, may do it. But I should not go as far as Falta in excluding from the diagnosis of infantilism those clinical conditions which depend on definite endocrine diseases, nor should I agree that such forms of infantilism as Lorain's show no evidence of being due to endocrine defect. I would hold Falta to his own definition of infantilism, and claim that if an individual showed them he should be regarded as a case of infantilism whether endocrine disease is present or not.

True dwarfism is distinguished from infantilism by the presence of adult proportions, though the absolute measurements are reduced—which would exclude conditions like achondroplasia—and by the absence of gonadal defects. If gigantism is due to an overacting anterior lobe of the pituitary, one would naturally expect dwarfism to be associated with its underaction, but one must admit that there is no evidence of this, nor of a pluriglandular defect. In the present state of our knowledge the origin of dwarfism is still to seek, though I have seen one case in which the stalk of the pituitary was gripped by approximation of the anterior and posterior clinoid processes.

### Classification.

The types of disturbed endocrine balance in childhood which I am prepared to recognise are as follows:

| | | |
|---|---|---|
| *Thyroid* | — | Cretinism. |
| *Pituitary:* | | |
| Anterior | + | General = gigantism. |
| | + | Partial = hemihypertrophy. |
| | — | Lorain type of infantilism. |
| Posterior | — | Diabetes insipidus. |
| Both lobes | — | Brissaud type of infantilism. *i.e.*, youthful Fröhlich type. |
| *Adrenal:* | | |
| Cortex | + | Sexual precocity. |
| | + | Infant Hercules type. |
| | — | Progeria. |
| *Parathyroid* | — | Tetany. |
| *Thymus* | + | Status lymphaticus. |

### The Thyroid.

It is unnecessary to discuss such a well-known condition as cretinism. But I should like to call attention to the minor degrees of hypothyroidism. It is worth while to look for its stigmata in children who fail to grow, who suffer persistently from nocturnal enuresis, who have night-terrors, or who suffer from relaxation of the articular ligaments, causing knock-knee, painful heel, flat-foot or lordosis. In my experience such symptoms may occur in children with minor degrees of hypothyroidism without any signs of mental slowness at all. This can be partly explained by the different function of the thyroid in children and adults. In the former it acts as the great stimulant to growth, but when this is complete its chief function is that of a katabolic agent. In the absence of this there is an accumulation of the products of incomplete combustion, which consequently infiltrate many tissues, including those of the central nervous system; hence the mental hebetude. Such an accumulation not occurring so readily in childhood, the mental symptoms are not so frequent as in adults with a mild degree of hypothyroidism. In my

experience childish obesity is more likely to be due to the pituitary than to the thyroid. The stigmata of hypothyroidism to which I allude are the disappearance of the outer half of the eyebrows, the malar flush, the heavy folds between the nose and cheeks, large tongue, supraclavicular pads of fat, stumpy hands and umbilical hernia. These are, of course, signs of cretinism, but if some of them are present, even in a minor degree, in association with some of the above symptoms, I think treatment by thyroid extract is indicated.

Next I should like to call attention to the frequency with which tonsillar sepsis may be a factor in producing hypothyroidism in childhood. We are familiar with the fact that tonsillar sepsis is likely to excite hyperthyroidism after puberty, but until the gland has experienced the activating effect of puberty it is apparently more easily exhausted than excited to overactivity. In other words, tonsillar sepsis makes demands on the thyroid which are apt to be under-compensated in the child and over-compensated in adults. Indeed, hyperthyroidism before puberty is extremely rare.

The connection between hypothyroidism and iodine starvation will be discussed in the chapter on the thyroid.

### THE PITUITARY.

Turning next to the pituitary, we find that overaction of the anterior lobe usually means overgrowth. In early life this overgrowth may be general, producing gigantism. I saw a case in which a boy reached a height of 6 ft. 5 in. at 16. Such individuals are, however, not strong, and often die in early life. A skiagram may show an enlarged pituitary fossa, and the palatal arch is high. The jaw is unduly prominent, while the hands and feet are disproportionately big. But the psychological condition is also abnormal, and I would sum up the peculiarities in this respect as a lack of inhibition and a craving for the limelight. As children they are naughty in a stupid sort of way, having no regard for truth and sometimes very little for other people's property. In their habits they are careless, if not actually dirty. Their craving for the limelight may be partially satisfied by their seeking the

company of their social inferiors, where they can shine more easily ; but it may also urge them to bizarre and even criminal acts, their lack of inhibitions making this all the easier for them. On the other hand, their sense of rhythm is often good—note that the pituitary is believed by some to have a special function with regard to rhythm—so that they may be musical, a gift which seems entirely independent of intellectual ability. It is, indeed, not uncommon to find musical ability coexisting with feeble inhibitions. Sometimes this overgrowth is partial, producing hemihypertrophy or even more localised changes. Keith has pointed out that in this localised overgrowth all the tissues will be involved—skin, hair, subcutaneous tissues, glands, muscles and bone. I recently saw a boy of 11 whose left leg was 2 inches longer than the right and $1\frac{1}{2}$ inches more in girth. The femur was slightly bowed outwards, so that the real increase in its length was greater than the apparent. There was thickening of the skin, with a large area of pigmentation ; the fat and superficial veins were also increased. There was no difference between the two arms, but the left side of the cranium was larger than the right, the occipital bone on that side distinctly overlapping the other.

I am afraid that so far no effective treatment can be suggested for this condition. With other glands coming into action at puberty, one may sometimes find that the discrepancy between the two sides becomes less marked, but this does not always occur. It seems that acromegaly and osteitis deformans are respectively the general and local expressions of overactivity of the anterior lobe of the pituitary in the adult ; and it is interesting to note that in this boy the femur on the affected side distinctly recalled that seen in osteitis deformans.

Conditions of pituitary deficiency in early life are much commoner than of pituitary overaction. As I have already said, some of these are temporary. Many cases of pubertal obesity fall into this group. In July, 1924, I was asked to see a boy of 13, who looked like a " Fröhlich " in all respects but one, for there were already signs of puberty. My advice consequently was to leave things to nature. By October he had shot up in growth, was not at all stout, and was exercising the captaincy of

his preparatory school with great success. What a triumph this might have appeared for a little uncritical organotherapy! Some cases of this sort show a mixed glandular defect. Thus in May, 1923, I saw a fat boy, aged 11, who suffered from night terrors, on waking from which he clutched at his throat as if he found difficulty in getting his breath. His tonsils and adenoids had been removed when he was 4. He tended to sleep on his face, as children with an enlarged thymus often do. The outer halves of his eyebrows were deficient and his mother had a somewhat hypothyroidic appearance. Yet his general appearance was that of hypopituitarism. The left testis was only just outside the inguinal ring. The tendency to overaction of the vagus was suggested in him by spasmodic croup in infancy, and in the family by one of his uncles being an asthmatic, and his only brother an epileptic. This multiple disturbance of the endocrine balance, in the direction of plus thymus and minus thyroid and pituitary, with the condition of the left testis, suggested a gonadal origin, which would probably be put right, or at least much improved, if puberty occurred normally. I saw him again seven months later, and found puberty just beginning, the testes normal and his general condition much improved. Obesity with signs of multiple glandular disturbances suggests a gonadal origin.

The Brissaud type of hypopituitarism is a more extreme condition. In 1923 I saw a good instance in a girl of 7. When 3 she was diagnosed by an eminent authority as a hopeless mental defective. I regarded her as an example of hypopituitarism. She had the "Dutch dolly" rounded face, with the clear skin and good colour which I associate with this type. But her eyebrows were almost completely absent. She had a high palatal arch and no upper lateral incisors had ever appeared. She was very fat, particularly along the back of the upper arms, below the scapulæ and on the thighs—a distribution which I regard as typical of this condition. The backs of the upper arms were reddened and she bruised very easily—also suggestive of hypopituitarism. She was very backward, and had poor control over herself physically and mentally; she was, indeed, only able to

walk with difficulty. I prescribed thyroid and pituitary together. I saw her in January, 1925, and found that she had improved greatly. She would then pass for a normally plump child of 9 as far as appearance goes. Her eyebrows were well developed and her lateral incisors had appeared. The arch of the palate had become wider, which presumably means that the base of the skull had expanded. Her control over her movements seemed normal, although, perhaps, she moved rather slowly. But she was still backward, and lacked the mental concentration necessary to learn. Her schoolmistress said that she had some sense of beauty, but very little sense of time, rhythm or music; that she seemed contented, but was not very affectionate; lazy, but never seemed sleepy or tired. I cannot deny that there may be an element of hypothyroidism here, but apart from the eyebrow sign her condition was much more like hypopituitarism. I lay special stress on the facies, the distribution of the fat, the reddened areas and the tendency to bruising in the diagnosis of this condition. The last symptom, that of ready bruising, appears to be due to polycythæmia, which, as I have pointed out, is very common in hypopituitarism. The absence of a sense of rhythm is an interesting psychological feature of this case. I saw her again a year later, when she was ten and found her condition much improved; she would have almost passed as a normal child.

I regard the Brissaud type as the pre-adolescent type of the Fröhlich syndrome, in which probably both anterior and posterior lobes are in defect.

The Lorain type of infantilism is a much rarer consequence of hypopituitarism. Here the pituitary lack displays itself chiefly in the small, delicately formed, slender skeleton, and sometimes in a tendency to baldness. It almost suggests that it is only that part of the pituitary which controls the growth of bone and hair which is involved. The legs are often relatively long, the trunk being very short—the opposite of the condition found in achondroplasia. There is no obesity. Mentally they appear to be normal, if rather hypersensitive. Here the anterior lobe alone appears to be involved.

As explained later, hypopituitarism may be a sign of

exhaustion following premature pituitary development. Thus early catamenia and a too early assumption of adult proportions may occur in patients who later show signs of hypopituitarism. Engelbach states that in hyperpituitarism the length from symphysis to vertex exceeds that from symphysis to soles, while in hypogonadism the reverse is the case. I am not convinced of the accuracy of this generalisation, but I am sure that in many cases of hypopituitarism the lower length is the greater. This may merely be another way of saying that hypopituitarism and hypogonadism are associated, as is certainly the case. When this lower length exceeds the upper before the age of 15, the patient is not likely to grow tall.

The association between defective action of the posterior lobe with diabetes insipidus will be discussed in the chapter on the pituitary, as it presents no features peculiar to childhood.

### THE ADRENALS.

In profound toxæmias or infections in childhood hæmorrhage may take place into the medulla, producing profound collapse, associated with convulsions, vomiting and purpura, a fatal issue generally occurring within 24 hours. It is not surprising that such hæmorrhage produces profound collapse, as it suddenly deprives the sympathetic of its chemical stimulant, adrenalin. Dudgeon has, indeed, suggested that purpura may be the acute manifestation of a symptom-complex, of which Addison's disease is the chronic form.

The effect of a tumour of the adrenal cortex in childhood is very striking. There is abnormal growth with obesity, precocious sexual maturity, and excessive growth of hair. It tends to produce virilism in whichever sex it occurs (and it is much commoner in females). The extraordinary condition of chloroma, described by Robert Hutchison, is due to a sarcoma of the adrenal with metastases which particularly affect the skull, and it displays its effect rather as a malignant tumour than by disturbing the endocrine balance.

Defect of the adrenal cortex in childhood produces that

rare condition termed progeria by Hastings Gilford. Here the child runs its life-cycle in a few years, and resembles the one described in the "Bab Ballads," who died "an enfeebled old dotard of five." Such facts as these strengthen my suggestion that in childhood the normal function of the adrenal cortex is that of a retarding agent, while playing a more active part at puberty and later. In excess it produces premature maturity; when in defect, the life force prematurely fades away and old age supervenes without maturity ever having been reached. For the due succession of the epochs of life, endocrine activities must wax, change and wane in due order.

### THE PARATHYROID.

Tetany will be discussed in a subsequent chapter.

Chronic parathyroid defect appeared to be the cause of the following symptoms in three children described by G. H. Clark—idiocy, depression, fibrillary twitchings in the muscles, jerking movements of the limbs, convulsions and inability to balance. Struck with the resemblance to the condition produced in animals by the removal of parathyroids, he treated them by parathyroid extract, with remarkable benefit. On discontinuing the drug the symptoms returned on two occasions in one case.

### THE THYMUS.

As to the thymus, as I have already stated, its rôle is normally limited to the infantile period. With the development of the gonads its activity ceases. The acquisition of the adult blood-picture and the disappearance of the thymus are generally simultaneous. Before that date lymphocytosis is a characteristic blood reaction, and the condition known as pseudo-leukæmia or splenic anæmia of infants cannot be produced after that time. This condition is probably simply the reaction of infantile blood to various severe toxæmias. The enlargement of the thymus in status lymphaticus is usually only a part of the general adenoid enlargement. It is tempting to regard this as part of an abormally sensitive reaction to foreign proteins, such as is usual to those whose vagus

response is increased. This would account for the liability of sufferers from status lymphaticus to paroxysmal dyspnœa, syncope and anaphylactic shock. Their extreme vulnerability is shown by their liability to sudden death from trivial causes. No doubt a contributory factor is the hypoplasia of the heart, which appears unable to develop properly under the cover of an enlarged thymus.

### MONGOLISM.

It will be observed that I have not included the Mongolian type of idiocy in this list of disturbed endocrine balance, because, although the thyroid is often deficient in this type, that is only one feature, and the origin of the condition lies deeper. There is a general failure to develop, in which the thyroid shares. Crookshank has recently rehabilitated and extended the ethnic classification of imbeciles propounded by my uncle, Dr. Langdon-Down, in 1866, according to which the Mongolian idiot shows atavism, a throw-back to what we are pleased to consider lower races. They may occur in families without a neuropathic history, and as they are apt to appear at the end of large families, when the mother is somewhat advanced in life, failure of reproductive power on her part may be the responsible cause.

The condition is not uncommon, and yet it is, in my experience, often overlooked. For that reason it is worth while to call attention to some of its most distinctive features. A facial diagnosis can usually be made, so characteristic are the eyes. The palpebral opening is narrow and almond-shaped, with its axis directed downward and inward ; at its inner corner there is an epicanthus, a fold of skin concealing the caruncle. This gives a distinctly Chinese aspect. Ptosis and strabismus are very common. The eyesight is not good, and polar cataract is rather common. The line of the eyebrows may be broken. The head is small and round and the sutures tend to remain open. The upper part of the ears overhang the lower, and Woolner's marks are usually to be seen. The skin is dry and there is a malar flush. The nose is snub and its root flattened out. The mouth is small, but the lips are large, the lower being

Hapsburg in type. The palatal arch is high and the uvula may be absent. The tongue is large with furrows on it like those of a gravy dish; it is apt to protrude. The child often makes a snorting, snuffling or purring sound. The teeth decay early and frequently show the small twisted or displaced upper lateral incisors already referred to. Not infrequently the upper lateral incisors are missing altogether. The abdomen is protuberant. The hands are short, broad and thick, and may show only one transverse fold on the palm. The index finger is shorter than the ring finger, and the little finger may be curved towards the radial aspect. The feet are also short and broad, with the cleft between the great and second toes continued on to the dorsum of the foot as a deep line. There may be blue patches of skin over the sacrum and in the groins, as in orangs. The bony articulations are lax, and there may be subluxation of the hip joints. The Mongol likes to sit cross-legged like a Turk.

Internally the cerebral cortex is diminished, with fewer convolutions and cortical cells. The thymus is enlarged, and congenital heart disease is not uncommon. Development is slow and is never completely normal psychically or mentally. Sexually they are undeveloped, yet puberty may actually begin earlier than usual. In such cases the whole life cycle is likely to be shortened. They are liable to catarrhal infections, rickets and tuberculosis, but are capable of living to a good age, though the mortality rate is high.

Temperamentally they are gentle and often affectionate. They are not usually irritable, but may sometimes have outbursts of temper and obstinacy. They are capable of a good deal of improvement by careful education and sympathetic handling. As they grow up they should be encouraged to lead as normal a life as possible, but they are seldom able to earn a living. I am satisfied that treatment by thyroid and pituitary extracts may help some of them to grow and develop, and that the earlier this treatment is initiated the greater the improvement. But although they present many of the stigmata of hypothyroidism, they never improve to the extent that a cretin does under treatment.

The special influence of the endocrine system in childhood to which I wish to call attention is the way in which it retards maturity to give time for further development, and utilises glands, subsequently katabolic in action, in the service of active growth. The balanced life is like a well-planned herbaceous border—to each season its appropriate flowers. For the due ordering of this we are much beholden to the endocrine system.

## CHAPTER III

## THE THYROID GLAND

Study of the endocrines started with the thyroid, and our knowledge of the pathology and treatment of diseases of this gland has always remained in advance of that of the rest of the endocrine system.

The thyroid gland is composed of closed vesicles containing colloid material, lined by a single layer of cubical epithelium, without any basement membrane. These vesicles are embedded in areolar tissue, in the interspaces of which colloid may also be seen, and in which the vessels and lymphatics lie. The structure of the parathyroids will be discussed later. Although now ductless, the thyroid originally opened by the thyro-glossal duct, through the foramen cæcum at the back of the tongue. Persistent remains of this duct may produce cysts in the middle line of the neck. The fact that the secretion of the gland originally entered the alimentary canal would account for the ease with which its active principle is absorbed when given by the mouth. This active principle has been isolated by Kendall, who considered it to be an iodine compound of indol, which he termed thyroxin; it has now been shown, however, by Harrington and Barger to be more closely related to tyrosin, containing 4 atoms of iodine attached to 2 linked benzene rings. It is, therefore, a body of comparatively simple composition and molecular weight. Like other outgrowths of the alimentary tract, it has both a sympathetic and a parasympathetic nerve supply, the former, which carries the chief secretory impulses, being derived from the superior cervical ganglion, the latter from the superior and inferior laryngeal branches of the vagus.

It alone of all the secretions formed by the body contains iodine, and the colloid in the vesicles may be looked upon as containing a reserve of iodine for the body. When the supply falls short, this emergency ration is

drawn on. As McCarrison puts it, "the thyroid is to the human body what the draught is to the fire." It stimulates growth in the young and assists the destruction and elimination of the protein molecule throughout life. It diminishes the storage of sugar and promotes the dehydration of fat. It also lowers the threshold of the response to sympathetic stimulation. In all these ways it is an active accelerator of metabolism, as can now be mathematically demonstrated by estimations of the basal metabolic rate. Its close connection with reproduction is shown by its physiological enlargement in the female at puberty, marriage and pregnancy, and by its partial involution at the climacteric. Moreover, thyroxin passes into the milk, the infant obtaining its chief supply in this way. It has been regarded by some as a distinctively feminine gland; at any rate it plays an important part in reproduction, which imposes a greater tax on the metabolism of the female. One hypothyroidic patient of mine, who benefited sufficiently from thyroid medication to become pregnant, developed eclampsia. The strain of pregnancy upon the thyroid should be remembered in ante-natal hygiene. The need for thyroxin in the proper nutrition of the central nervous system and of the skin and its appendages is well known. Thyroxin also plays an important part in the reaction against bacterial infections.

When the iodine content of the thyroid falls below 0·1% of its dried weight, the gland begins to enlarge. This occurs also as soon as three-quarters of the gland have been removed. Clearly, therefore, a considerable degree of iodine shortage has occurred before it manifests itself by thyroid enlargement.

"Why the Sea is Salt" is the title of an old fairy tale. We recognise to-day that the quern of that story, which grinds salt into the sea, is the river which washes soluble salts out of the earth and carries them down to the sea. Hence the sea becomes gradually more salt at the expense of the land. Iodides are soluble salts and the effect of their removal naturally tells on the mountain valleys sooner than on the lowlands. Cretinism and goitre are much commoner in the former districts, and it is naturally tempting to look upon such conditions as due to iodine

starvation. But, as we shall see, the matter is not quite so simple as that.

### GOITRE.

The thyroid may undergo simple parenchymatous enlargement, with or without increase of colloid, or cystic degeneration. Enlargement may also be due to adenomata. The liability of goitre to be endemic has long been recognised, *e.g.*, in Derbyshire and in high-lying Swiss valleys. Its association with chalky districts is not to be explained by the resulting hardness of the water, but by the permeability of the soil, which readily allows of infection of the water supply, as shown by McCarrison. Once established in a district it is apt to spread. Thus I have been much struck with the increasing frequency of goitre at the eastern end of the Chilterns, and its spread into the greensand to the north of the chalk, which is also permeable. On passing into the clay districts in Essex, however, the disease becomes comparatively rare. A systematic study of the incidence of goitre in relation to geographical strata and water supply would yield valuable results to public health. Whatever the exciting cause may be, it does not appear to pass through a porcelain filter, while fæcal contamination of the water supply renders it much more likely to induce goitre. A bacterial cause is therefore probable, though whether by direct infection of the bowel or because such bacteria destroy the small amount of iodine normally present in the water, is not yet certain. Sporadic cases are less easy to explain, but appear more likely to occur in the children of hypothyroidic parents. The disease usually starts in childhood or early life, and in non-goitrous districts attacks females more frequently than males. It is usually insidious in onset. It has been claimed by some observers, particularly in America, that administration of iodine, whether in the public water supply or in the form of iodized chocolate or by adding iodide to the table salt, has greatly diminished the incidence of endemic goitre. Thus 30% to 65% of the girls in the Mississippi Valley were found to be suffering from goitre, and it is stated that the addition of 2 lb. of sodium iodide to every 100,000 gallons of water in the reservoir

greatly reduced the proportion thus affected. Good results have also been reported from Switzerland. On the other hand, the experience of such methods in England has not been so favourable. Dr. Turton has kindly informed me that at Heanor, in Derbyshire, in conjunction with Ilkeston, they tried iodisation of the public water supply from December, 1924, to January, 1926, when the plan was abandoned as useless. There was actually a decided increase of enlarged thyroids in the school children. It does not appear safe to administer iodine indiscriminately to children, many of whom are at the age of puberty. But prior to 1902 surface water and well water were used in these districts, and then endemic goitre was certainly commoner. This suggests that, after all, the theory of an infection may be correct.

The question is complicated by the fact that the colloid goitres of adolescence may be associated with normal, increased or diminished function. Gardiner Hill, Brett and Forrest-Smith (*Quarterly Journal of Medicine*, 1925, Vol. 18, p. 133) found the function of the gland to be normal in 42% of such cases. It should be observed that in this event the goitre usually appears before the catamenia, whereas if function is disturbed the goitre never appears till after. There was increased thyroid activity in 32%. In these the weight was usually below the average for the age, the catamenia tended to be delayed, irregular or scanty. Diminished function of the gland went with the goitre in 26%. In such cases the weight was usually above the average and the catamenia tended to be excessive. They found that the basal metabolic rate corresponded exactly with the clinical findings, so that it is evidently the most accurate guide. The blood sugar curve, as might be expected, was normal in those with normal function. In those with increased function, the curve showed a delayed fall, while in those with diminished function there was a delayed rise and a slightly delayed fall. Evidently we can only reach a conclusion as to the line of treatment to be followed after careful consideration of all the factors. If function is diminished, thyroid extract is the best treatment; if it is increased, very cautious administration of iodine on the lines discussed under exophthalmic goitre should be

tried. Here too large a dose of iodine may undoubtedly do harm. In the cases with normal function I also usually give small doses of iodine, but the question of the water supply must always be considered. Where the quality of this is in any doubt, it should be boiled.

Occasionally pressure symptoms develop, particularly if the goitre extends behind the sternum, when it may produce dyspnœa, congestion of the veins in the neck, and interference with the recurrent laryngeal nerve, leading to stridor and hoarseness, or with the cervical sympathetic, leading to dilatation of the pupil and irregular sweating on the affected side. Pressure on the vagus, producing slowing of the pulse or syncopal attacks, is much rarer in my experience. In the neck the goitre may extend behind the trachea, producing dyspnœa and dysphagia, or it may involve the spinal accessory nerve.

A simple goitre, after existing for months, or more usually for years, may develop certain signs and symptoms of hyperthyroidism, a condition known as toxæmic goitre. In my experience this is most apt to occur when there are multiple adenomata in the glands. Thus in one case of such adenomata which had existed for several years without producing any symptoms beyond the enlargement, the patient developed tremors and her blood sugar was found to be raised. The basal metabolic rate was found to be increased 50%. Under medical treatment this was reduced to + 35%, but a fortnight later it was still + 32%. Mr. Harold Wilson accordingly removed the adenomata, after which the basal metabolic rate fell to normal and the tremors disappeared.

Whereas in true exophthalmic goitre the first symptom is usually exhaustion, and nervous symptoms either precede or follow quickly on the thyroid enlargement, there is always a considerable interval between the enlargement and the nervous symptoms in toxæmic goitre. I am inclined to advise operation in such cases when there is a definite adenoma, as the results are good. Cases of diffuse enlargement with hyperthyroidism should be treated as for exophthalmic goitre.

Simple goitre is usually very chronic, and in many instances produces no ill effects beyond the disfigurement. Only those cases which appear rapidly are likely to sub-

side to any marked degree. When fibrous or cystic changes have occurred, resolution is not possible. Therefore treatment should be early.

### HYPOTHYROIDISM.

Myxœdema and cretinism are so well known that it is not necessary to describe them in detail. Their recognition is a striking instance of the advantages of combined experimental and clinical observations. **Myxœdema** is much commoner in women than in men, and is most likely to occur shortly before or after the menopause. In men it may occur both earlier and later in life than in women. The cause is unknown, but may sometimes be due to exhaustion of the defensive power of the gland by some toxic process. The tendency of thyroid derangements certainly appears to run in families. The gland is diminished in size, becomes hard and pale, and is the seat of a connective-tissue overgrowth with atrophy of the vesicles.

The onset of myxœdema is quite gradual. The well-developed forms of a disease are generally recognised before the minor degrees. But chiefly owing to the work of Hertoghe we now know that slighter forms of hypothyroidism are quite common, and a description of these may serve as an account of the earlier stages of myxœdema. The accumulation of material that should be katabolised may cause submucous infiltration of the eustachian tubes and accessory sinuses, leading to headache, giddiness, somnolence and a sense of fulness in the head and ears. A number of manifestations of hypothyroidism are attributed to rheumatism, although really due to myxœdematous infiltration of ligaments and fasciæ, producing knock-knee, painful heel, flat foot and lordosis. The hand becomes lax and flabby, feeling, as Hertoghe says, like a glove stuffed with clay. The hair becomes scanty. A very helpful sign of hypothyroidism is the disappearance of the outer half of the eyebrows. The association of this with " rheumatic " symptoms should suggest the administration of thyroid extract. Indeed there is some evidence that true rheumatism flourishes best on a hypothyroidic soil. Nocturnal enuresis has been shown to be sometimes due to the same cause, partly because

desquamation of the epithelium of the bladder renders it more irritable, and partly because of the deep somnolence. Infiltration of the nerve centres causes mental slowness, loss of memory, and difficulty in expressing ideas. As the condition develops the skin becomes harsh and dry and the eyelids baggy. There is a malar flush, which with the fullness of the cheeks above the naso-labial fold gives a very characteristic appearance. Supraclavicular pads of fat develop. The hands become thick and spade-like; the legs swell, but do not pit on pressure. Atheroma is not uncommon. Constipation is the rule and may be very troublesome. There is a tendency to amenorrhœa, though menorhagia may occur. Basal matabolism may be reduced by 40% or more, and the temperature is subnormal. This explains the aggravation of the symptoms in cold weather. The liability of hypothyroidic individuals to chilblains is well known, and a condition like Raynaud's disease is not uncommon. It will usually be found that there is then a well-marked intestinal toxæmia, generally the result of definite visceroptosis, which often exhausts the thyroid, while also affecting the vessels. The subject of hypothyroidism improves during pregnancy and relapses during lactation. This is not surprising in view of the stimulating effect of pregnancy on the gland and the drainage of its secretion into the milk. But in spite of this it is wise to give such individuals thyroid treatment during pregnancy, since it diminishes both the liability to abortion and the subsequent exhaustion of the gland. Widal has recorded an interesting case of the association of asthma and myxœdema. A girl aged 14 developed asthma, which recurred until she was 24. She then became pregnant, and the asthma ceased until the periods returned. She continued to suffer from asthma and from catarrh with morning dyspnœa, excited by roses, until she was 37, when there was a premature climacteric. The paroxysms of asthma ceased, but she remained sensitive to roses. She then became myxœdematous and was treated on three occasions by a course of thyroid extract. Each time the myxœdema cleared up, and with it the morning dyspnœa and the sensitiveness to roses. This case can be explained on the theory of antagonism

between the parasympathetic and the sympathetic. The asthmatic has a relatively overacting vagus, but this may be due to an actual diminution of sympathetic activity, from hypothyroidism, which deprives the sympathetic of a stimulant. This patient betrayed hypothyroidism by a premature climacteric, and by ultimately developing myxœdema. When the thyroid was stimulated by pregnancy or when thyroid extract was given, the balance was, at any rate, partially improved.

**Cretinism** is due to congenital thyroid insufficiency, and is common in goitrous areas, or in the offspring of goitrous or hypothyroidic parents. That is to say, it may be endemic or sporadic. The patient is stunted, with retarded development and delayed ossification of the bones. The general appearance recalls myxœdema, the nose is flat and the nostrils large, the hair thin. The tongue is large and often protrudes between the lips. The thyroid gland is apt to be goitrous, and in any case shows extensive atrophy of its secreting epithelium. The abdomen is distended and umbilical hernia is common. Sexual and mental development are much retarded. The disposition is placid, and facile in accepting a change of environment. Treatment to be successful must be adopted early.

The doses of thyroid extract formerly employed in all forms of hypothyroidism were, as pointed out by Leonard Williams, too large. Palpitations and tachycardia were not uncommon results, and a condition resembling Graves' disease has been produced. Glycosuria has repeatedly been observed.

It is better to state doses in terms of the fresh extract, for thyroideum siccum is five times as strong, which does not admit of such ready variation of the dosage. The *British Pharmaceutical Codex* directs that, except when the dried extract is specifically prescribed, the drug shall be dispensed in terms of the fresh extract, to avoid risks of over-dosage. I had a patient who improved on gr. $\frac{1}{4}$ twice a day, but who proved intolerant of three such doses a day. But usually one can start with gr. $\frac{1}{2}$ twice a day and increase it each week by $\frac{1}{2}$ gr. until a dose of 2 grs. three times a day is reached. Larger doses are not often

required. Sometimes a high degree of tolerance is shown. Thus a patient suffering from a minor degree of hypothyroidism had been taking 15 grs. a day, and maintained that if she took less than 8 grs. a day she could not sleep! A careful watch for glycosuria should be kept on patients taking thyroid extract. I saw one of the first cases of myxœdema that was treated in this country by thyroid extract, who, after thirty years of treatment, developed true diabetes. But this must be very rare, though slight glycosuria is fairly common.

### HYPERTHYROIDISM.

All degrees of this may exist, from simple goitre with toxæmic symptoms up to fully developed Graves' disease. More and more I am convinced that Graves' disease is produced by the combined effects of toxic and psychic factors. It has been well said that the majority of cases are due to "sex and sepsis."

The septic foci are most often to be found in the nasopharynx, particularly in the tonsils. The antrum has been responsible in several of my cases, particularly for incomplete forms of the disease, in which there was loss of flesh, tachycardia and tremors, and sometimes glycosuria, but without ocular signs or enlargement of the thyroid. The condition may be due to dental sepsis, though less frequently than to tonsillar infections. I saw a patient who had had the right lobe of his thyroid removed in 1908, and three separate operations performed subsequently for ligature of the arteries on the other side, but who still had active Graves' disease. I found he had a bridge right across the front of his upper jaw. The gums were leaden in hue and a skiagram revealed extensive absorption of bone. The grave oral sepsis was all the more dangerous because of the rigid metal case in which it was enclosed. In one case of mine Graves' disease followed pericarditis, but probably both conditions were due to the same cause, for there is good reason for regarding acute rheumatism as due to alimentary streptococci of altered virulence. Intestinal toxæmia may be an exciting cause. All these causes are comprehensible now that we know that the tonsil and thyroid arise from similar structures, that the active principle

of the latter is an aromatic body, and that the thyroid is a defensive mechanism of the body against infection.

But whether a toxic focus results in Graves' disease or no depends largely on the emotional state. Cannon's oft-quoted experiments on cats show the importance of sympathetic stimulation in producing thyroid enlargement. He joined the central end of the phrenic to the peripheral end of the cervical sympathetic nerve on one side, so that the gland was stimulated with every breath. This resulted in tachycardia, increased excitability, loose motions, exophthalmos on the side of the operation and a great increase in metabolism. A sudden shock or a prolonged strain on the emotional nervous system must lead to overstimulation of the thyroid, especially if the motor expression of the emotion is thwarted. Thus fear has a marked influence in exciting hyperthyroidism, as was well seen during the air-raids on London. Self-controlled people, who, nevertheless, suffered acutely, repressed their impulses from the motor to the vegetative level, and received their reward in hyperthyroidism. The same thing was observed after the Kishineff massacres and the San Francisco earthquakes.

But hyperthyroidism is particularly apt to occur when the emotional distress has a sexual origin. This adds to the difficulty in detecting the cause, since it is not usually a matter of advertisement. I had the opportunity of watching the case of an unmarried lady, who was entrusted with the care of her niece between the ages of 4 and 17. The girl's parents were Anglo-Indians, and when she grew up they sent for her to go back to India. The aunt was greatly distressed, for her whole emotional life centred round the girl. Within six weeks of her departure the patient, who had reached an age which precluded the possibility of children of her own, developed marked Graves' disease.

The thyroid gland shows a general enlargement which may be very considerable. It is very vascular, and the vesicles are lined with long columnar cells, so increased in number that they are often folded into the lumen, leaving no room for any colloid to be retained there. A resting stage for the gland becomes impossible, and the abundant secretion is hurried into the circulation. A

vicious circle is started which is hard to break, since thyroid secretion lowers the threshold to sympathetic stimulation, and the sympathetic stimulates the thyroid.

The earliest symptom is usually one of persistent fatigue, as G. R. Murray pointed out. The four cardinal signs in a fully-developed case are exophthalmos, enlargement of the thyroid, tachycardia and tremors, but any one of these may be missing. The nervous symptoms may appear before the gland enlarges, and in any case will not be long delayed. Associated with the exophthalmos there will probably be: (1) Joffroy's sign—the failure of the frontalis muscle to act, so that horizontal wrinkling of the forehead is impossible. Indeed, the skin of the forehead appears to be drawn tight over the bone. (2) Von Graefe's sign—the lagging of the upper eyelids on looking down, which leaves the white sclerotic visible above the iris. (3) Stellwag's sign—the widened palpebral angle with imperfect conjunctival reflex. (4) Moebius' sign—the failure of regular convergence of the eyes. The extreme proptosis and the failure of the conjunctival reflex may lead to corneal ulceration. These ocular signs are no longer attributed to spasm of the plain muscle of Müller. The intra-orbital fat is increased, but the prominence of the eyes is largely due to the relaxed condition of the blood vessels, and it is much less noticeable after death. One eye may be more prominent than the other. The corners of the mouth turn down, and the whole aspect is one of continuous fear.

The enlarged thyroid feels soft and uniformly enlarged, and a systolic bruit is audible over it. It moves on deglutition unless the gland has become fixed by invading behind the trachea or beneath the sternum. The thymus is also enlarged, and may give rise to retrosternal dullness. This is the more surprising since the thymus should have atrophied before the age at which Graves' disease occurs. But the thyroid itself, in extending behind the sternum, may produce similar dullness.

Tachycardia is one of the most constant signs, and the pulse frequency so often exceeds 120 a minute that it cannot be attributed to mere loss of vagus control. The tremors are fine intention tremors, and are best seen in the hands when the arms are fully extended.

Diarrhœa, perspirations and areas of pigmentation of the skin are common. The diarrhœa may be so severe as to cause death, and I have seen leucoderma follow the pigmentation.

The basal metabolic rate is considerably raised, and may be 100% in excess of normal. It provides one of the best indices to the progress of the patient. Whitridge Davis and Eason have pointed out that the pulse pressure, *i.e.*, the difference between systolic and diastolic blood pressures, is increased in range. Normally this should be 40, and the increase is roughly proportional to the increased metabolic rate, thus providing a simple test for its presence. I have, however, found a normal pulse pressure with an increased basal metabolic rate.

In few of my cases has the blood sugar curve been normal. As a rule there is no resting hyperglycæmia, but generally a sharp rise, an hour after 50 grammes of dextrose are given, and a delayed fall. Thus in one case the fasting blood sugar was 0·069%, rising after an hour to 0·323%, and keeping at 0·282% at the end of an hour and a half. Yet there was no glycosuria at this stage of the disease because the kidney threshold for the excretion of sugar was raised. As the patient improved she had occasional glycosuria, presumably because the kidney threshold fell faster than the glycæmia. Alarm is, therefore, unnecessary if glycosuria occasionally occurs, as long as the patient is improving in other respects. Hyperglycæmia is much commoner in Graves' disease than glycosuria. In one severe and ultimately fatal case the blood sugar rose to 0·27% an hour after 50 grammes of dextrose. There was no glycosuria then, though it occurred later under emotional disturbance. This enabled me to detect the psychic factor in his condition. I believe hyperglycæmia to be a factor in the production of the increased metabolic rate. Profound wasting may result, as in this case, where more than half of the total body weight was lost.

A very serious complication is auricular fibrillation, which is much commoner than was formerly supposed. Thyroid secretion accelerates the heart without augmenting the force of the beat. Presumably this exhausts the auricular muscle. This leads to dilatation and valvular

incompetence. Ultimately myocardial degeneration follows, which may result in auricular fibrillation. It is probable that extension of the fibrillation to the ventricle is sometimes the cause of sudden death after operation for Graves' disease.

The changes in the blood pressure have been studied by Goodall and Rogers. They describe three stages :—

(1) **A Preliminary Stage of Hypertension.** This is relatively short, associated with the onset of the disease, and is probably due to peripheral vasoconstriction induced by the action of the exciting stimulus on the suprarenal. It is most easily demonstrated in cases that come on after shock, acute anxiety, or fright.

(2) **A Stage of Hypotension.** This is relatively long, lasting for months or even years. The blood pressure is below the physiological level, the lowered tension being due to vasodilatation induced by a depressor substance secreted by the hyperactive thyroid. It is during this stage that the majority of patients seek advice. It may be regarded as the best stage for operation. The heart is usually soft, atonic and more or less dilated, with reflux at one or perhaps both auriculo-ventricular valves.

(3) **A Stage of Secondary Hypertension.** This is a period of gradually rising pressure, which succeeds the second stage after a varying length of time, usually some years, and appears to be associated with two conditions : (*a*) a reduction of the excessive thyroid activity, with a consequent relative increase in that of the suprarenal ; (*b*) some secondary change in the cardiovascular system, such as cardiac hypertrophy.

In each phase, and particularly in the second, diurnal variations are considerable. After operation an immediate and definite but temporary rise in blood pressure occurs, which may reach double the pressure before operation. The effect of this, in enormously increasing the work of an already partly exhausted myocardium, and perhaps inducing ventricular fibrillation, must be borne in mind in considering operation. Routine study of blood pressure has proved of great value in the selection of suitable cases.

The catamenia are usually irregular and scanty, and

amenorrhœa may occur. The mental state is one of unrest and irritability, which may become extreme, reaching an instability characterized by suicidal or even homicidal tendencies. Actual insanity is not rare. The psychoneuroses connected with hyperthyroidism are discussed later.

Since adrenalin also stimulates the sympathetic, it might be expected that patients with hyperthyroidism would show an undue sensitiveness to this hormone. Two biochemical tests for hyperthyroidism have been based on this idea.

(a) **Loewi Mydriasis Test.** This was originally introduced as a test for pancreatic disease. If a drop of 1 in 1,000 solution of adrenalin chloride is instilled into the conjunctival sac, and another drop five minutes later, the pupil will dilate within half an hour if the pancreas is inadequate. The dilatation may be eccentric. The test is based on the antagonism between the internal secretions of the pancreas and adrenals, which normally balance one another. But it was then found that excess of thyroid secretion by sensitising the sympathetic nerve endings to adrenalin caused this reaction to occur in the absence of any pancreatic defect. This test is of some value in the diagnosis of hyperthyroidism.

(b) **Götsch's Test.** Eight minims of the 1 : 1,000 solution, diluted with an equal amount of sterile water, are injected hypodermically into the arm. Some observers prefer an intradermal injection. The arm around the point of injection immediately blanches, and at the margin of this there is a red areola gradually shading off into the normal skin colour. In about half an hour the centre of the area becomes lilac or lavender in colour, and from $1\frac{1}{2}$ to 2 hours the red areola becomes lavender while the central area fades. The lavender part of the areola is the characteristic part of the test, and lasts for about four hours after injection. The local reaction may be accompanied by increased symptoms of hyperthyroidism, such as tachycardia, a rise in systolic blood pressure, with a fall in the diastolic, exaggerated tremor, fear and anxiety. Golla describes a case in which the patient felt the sensations without the emotion of fear and distress after the injection. On mentioning a disagreeable topic,

however, there was an outburst of emotionalism. The diagnostic value of this test is by no means assured.

The course of Graves' disease is very variable. The slighter cases generally do well under appropriate treatment. Probably about half the cases recover more or less completely, but symptoms of thyroid exhaustion may appear subsequently in some of these, so that a condition not unlike myxœdema develops. In others the disease becomes chronic, and may lead to insanity. I have seen true diabetes develop, and such cases, though temporarily improving under treatment, have ultimately done badly. Auricular fibrillation, diarrhœa, and exhaustion, are the commonest causes of death. According to Leyton the mortality rate is less than 12%.

The medical treatment of Graves' disease may be summed up as physical and mental rest, in the widest sense, with elimination of all toxic factors as far as possible, administration of iodine and quinine hydrobromide, and attention to symptoms as they arise. The earlier and more efficient the medical treatment, the less will partial thyroidectomy be required. Septic tonsils must be enucleated, oral sepsis must be treated, and intestinal disinfectants may be called for. Complete rest in bed for 6 to 8 weeks or even longer is an essential part of treatment. Psychical causes must be alleviated where practicable, but from the nature of the case this is generally only possible by sublimation, and the patients' mentality will not permit of this, at any rate until the physical condition improves.

Of recent years iodine has been strongly recommended for this condition, and it is certainly a most valuable drug if carefully handled. At first sight it seems extraordinary that the same drug should be used in both hypothyroidism and hyperthyroidism. It is probable that the enlargement of the gland in the former condition is often symptomatic of iodine starvation, while in the latter condition the secretion, though increased in amount, is not adequately saturated with iodine. Thus opinion is tending to agreement with those who have looked upon " hyperthyroidism " as a dysthyroidism. This view has been advanced by Ellis. The active principle of the thyroid, thyroxin, which is chemically related to tyrosin,

should contain 65% of iodine, distributed as four atoms round the two benzene rings it contains. Now iodine seems necessary to the resting state of the gland, so, if this is lacking, the gland is in a condition of unrest and the secretion abnormal. If iodine is supplied, the symptoms improve until enough has been given to saturate the thyroxin with its four atoms, but if the dose is then maintained at the same level, after saturation has been reached, there will be too much iodine, and the symptoms begin to be aggravated again. This suggests that excess of iodine may stimulate the further production of thyroxin. It has been urged that the absence of indican in the urine is of bad prognosis in exophthalmic goitre, but I have not been able to convince myself of this. On the contrary, it seems to me that excessive intestinal putrefaction may play a part in causing hyperthyroidism, and Nott (*British Medical Journal*, 1925, Vol. 1, p. 443) has recommended intestinal douches of 1 grain potassium of permanganate in 1½ pints of water as a useful disinfectant. The treatment has been used both where the thyroid appears to be in excess or in defect. The common factor lies in the intestinal toxæmia, the difference in the response of the gland to that toxæmia.

Insulin was suggested by R. D. Lawrence for the treatment of Graves' disease. It is rational because of the antagonistic effects of insulin and thyroxin on the blood sugar and general metabolism. In my opinion it is particularly useful where the loss of weight cannot be controlled. Five units of insulin should be injected daily, and 15 grammes of dextrose given by the mouth at the same time. If this is well borne but is insufficient to prevent loss of weight, the doses both of insulin and dextrose should be doubled.

Since McCarrison introduced quinine hydrobromide in the treatment of this disease I have used it extensively, and regard it as one of the best drugs we have for the purpose after iodine, particularly in the milder cases. A man will usually tolerate 5 grains three times a day, but with a woman it is better to start with 3 grains. It may be reinforced with 20 to 40 minims of dilute hydrobromic acid, and given with some syrup of orange in an ounce of chloroform water. McCarrison advises 1 gr. of mercury and

chalk daily as an adjuvant. Digitalis may help to control the tachycardia and thus to avoid fibrillation or to relieve its effects, should it occur. But as digitalis does not restore a normal auricular rhythm, merely preventing irregular conduction to the ventricle, quinidine may be given a trial with advantage. Indeed, quinidine has been recommended for Graves' disease, though I have not found it so useful as quinine hydrobromide in the absence of fibrillation. It is well to give an initial dose of 2 grs. of the sulphate of quinidine to guard against idiosyncrasy, and then to work up to 4 to 7 grains three times a day, reducing the dose, as soon as a normal rhythm is restored, to the smallest amount which will maintain it.

As lack of vitamins leads to diminished thyroid secretion, it has been suggested that in Graves' disease the diet should be free from fat, so as to exclude the fat-soluble vitamins. I have not been impressed with the results of this treatment. As meat presumably implies flesh from animals in full thyroid activity, it has been recommended that this should not be allowed. A similar argument would apply to milk, and I doubt whether these restrictions are of much value.

Direct diminution of thyroid secretion by operation or irradiation aims at breaking the vicious circle referred to above. The best guide as to the necessity for such measures is the basal metabolic rate. Means and Aub consider that, if drugs and X-rays fail to reduce this to within 20% of normal, there is a plain call for surgery, unless there is some definite contra-indication, such as a rising metabolic rate in spite of complete rest, when they regard the surgeon's intervention as fraught with peril. But it is usually considered advisable to decide between X-rays and surgery, since a gland which has been irradiated has been found more difficult to treat surgically. Barker's method is to use 5 milliamperes of current through a Coolidge tube for 3 minutes, the resistance being equal to a 10-inch spark measured between points, the rays being filtered through 3 millimetres of aluminium. The anode is placed 8 inches from the skin, the dose given through each area, and the treatment repeated every four weeks. He finds that the subjective symptoms are

the first to be relieved. The patient begins to feel less nervous, has less palpitation, sleeps better, and is less irritable and tired. The first of the objective signs to improve is the tachycardia. When the patient feels better the interval between the doses is increased to six weeks, and finally to eight. If there is any return of the symptoms the interval may be shortened. Probably six to eight doses will be required at four-week intervals, which are then lengthened from eight to twelve weeks, and the patient is kept under observation for about a year. He does not mention the risk of producing telangiectases, which certainly exists. Moreover, irradiation sometimes aggravates the condition, at any rate temporarily. Aikens (*Canadian Practitioner and Review*, 1920, Vol. XIV, p. 329), advocates the advantages of treatment by radium screened to prevent the beta rays getting through, but allowing the gamma rays to penetrate. The dosage he uses is 150–360 milligram hours for the first treatment, and 50–150 milligram hours subsequently. But I find myself resorting less to irradiation and more to operation.

The results of partial thyroidectomy are often brilliant, but even in skilled hands the operation is by no means free from risk, even in carefully selected cases. Operation should, therefore, only be considered when the general condition fails to improve after some weeks of thorough medical treatment.

**Thyroid Crises.** A thyroid crisis is a rare but dangerous complication of Graves' disease. The patient suddenly passes into a state of acute hyperthyroidism, with an extremely rapid, almost uncountable pulse. It may be induced by some intercurrent infection. American observers advise large doses of iodine, and I have given 10 minims of tincture of iodine every 4 hours for a time in this condition with benefit. Even larger doses have been given. No other treatment appears to be of any avail.

**Thyroid Instability.** This is the name given by Leopold-Levi and Rothschild. Here there are spurts of hyperthyroidism imposed on a background of myxœdema. It is a condition of irritable weakness, comparable to that seen in the occupation neuroses, and it calls for the

cautious administration of thyroid extract to steady the fluctuation secretion. In one such case the patient was rapidly increasing in weight, but had attacks of tachycardia. Under this treatment she soon recovered. But in another the picture gradually became that of hyperthyroidism.

**Intermittent Swelling of the Thyroid in Certain Nerve Storms.** Such cases are presumably allied to thyroid instability, but they illustrate the close association between the thyroid gland and the emotional nervous system. I may quote three instances: (1) A lady of fifty was brought to see me because she suffered from periods of depression, followed by periods of excitement, tachycardia and tremors, in which the thyroid swelled. Hysterectomy had been performed $4\frac{1}{2}$ years before, and a cystic adenoma had been removed from her thyroid ten years ago. She had no glycosuria after 100 grammes of dextrose and, unlike an ordinary case of hyperthyroidism, her urinary diastase was rather high. This was not observed, however, during a period of excitement. The effect of quinine hydrobromide was to cut out the periods of excitement, but to leave the periods of depression. Careful search was made in this case for a toxic factor, without success. I regard such cases, which are not uncommon, as allied to manic-depressive psychoses, with secondary endocrine disturbance. (2) A girl of twenty was admitted to hospital under my care with the history that some eight months previously her ovaries and tubes had been removed on account of tuberculous disease. After this she became fairer in complexion and put on weight considerably. She suffered from hot flushes. Her thyroid had been rather full before the operation, but this had been less noticeable since, except during the attacks for which she was admitted to hospital. These occurred every three to four days. There was no aura, and consciousness was almost, but not completely, lost. She flushed and choked while the pulse and expiration quickened very much. The attacks lasted about six minutes and ended quickly, though the pulse-rate subsided more slowly. The thyroid swelled noticeably in the attacks, and she passed a small amount of sugar then, but not at other times.

Under bromide and ovarian extract the attacks ceased. Then the latter only was given, and in spite of having no bromide the attacks were few and far between. Her weight has fallen considerably; the hot flushes have ceased, and her general condition has greatly improved. (3) A boy of eighteen had been subject to petit mal for three months following an accident. Thirteen years later he had a recurrence of these attacks after another accident in 1917. In July, 1921, he had malaria, after which his petit mal assumed some new features; on recovering from a brief unconsciousness he became restless and excited, complained of difficulty in swallowing and his thyroid swelled. On one occasion it was only the left lobe that enlarged. He was a very intelligent man, and expressed himself as feeling completely disorientated for about ten minutes by an attack. A curious feature was his bradycardia, the pulse-rate varying from 48 to 52. Even when his temperature rose to 104° in an attack of malaria his pulse only went up to 64. Yet on vigorous exercise the pulse-rate rose to 96 for a short time. I associated this bradycardia with his epilepsy. There was a large element of matrimonial trouble. On quinine hydrobromide, and then on potassium bromide, he has kept free from attacks.

It is interesting to note that the first two cases had their endocrine balance upset by the induction of an artificial climacteric, one in early life, the other shortly before the time when it would have normally occurred. I should like to call special attention to the benefit derived from the ovarian extract in apparently restoring the endocrine balance in the second case. In the third case no doubt the thyroid specially suffered in the outbreak of excitement, because it was already irritated by an infection, namely, malaria. The absence of tachycardia with emotional excitement suggests that vagotonia played a part in this case. But all three cases illustrate the influence of emotional excitement on the thyroid.

## CHAPTER IV

## THE PARATHYROIDS

The first clear description of the parathyroids was given by Sandström in 1880. He showed that they varied very much in arrangement in different animals. In man the two lower parathyroids at least lie outside the capsule of the thyroid, close to its posterior border, near the spot where the inferior thyroid artery breaks up into branches prior to entering the gland; but there are other fragments of parathyroid tissue. It has long been known that the operation of thyroidectomy has much more serious results in carnivora than in herbivora. Gley explained this by the varying position of the parathyroids, believing that, if this was such that they were perforce removed with the thyroid, extirpation of the thyroid was fatal, not otherwise. The occurrence of tetany was also held to depend on removal of the parathyroids with the thyroid.

Then followed a phase in which the parathyroids were regarded merely as part of the thyroid apparatus, which had not developed vesicles, but which had essentially the same function. This position has been abandoned by most authorities for the following reasons :—

(1) Although there is accessory thyroid tissue in variable positions, the true parathyroids are constant in position for each species.

(2) Parathyroid tissue has a constant histological structure, which has recently been well described by Dunhill. It consists of (*a*) polygonal or rounded cells with dark nuclei, but whose protoplasm scarcely stains at all; and (*b*) islands of larger polygonal cells with granular, brightly stained eosinophilous protoplasm.

(3) Collip has recently isolated an active hormone from the parathyroids, by injection of which he was able to

prevent or control tetany in dogs after removal of these glands. Their blood calcium could thus be kept within normal limits. If the hormone were given to normal animals the blood calcium could be raised. If it be raised too much, vomiting and diarrhœa result, going on to hæmatemesis and melæna, and the animal may die.

There is, therefore, ample anatomical, histological and chemical evidence that the parathyroids are distinct from the thyroids in structure and function. All this fits in with Korenchevsky's experiments, in which he destroyed the two main parathyroids in rats with a fine electric cautery without injury to the thyroid. In a group of 25 rats about two will die in spasms after the operation. In these almost all the parathyroid tissue will be contained in these structures. The others have sufficient elsewhere to support life, but they become cachectic and can at any time be thrown into tetany.

MacCullum and Voegtlin find in parathyroidectomised animals during tetany (*a*) a marked reduction of the calcium content of the blood and nervous tissues, and (*b*) an increased output of calcium in the urine and fæces. Injection of calcium salts or parathyroid transplantation have checked the spasms, and taking these facts into conjunction with Collip's observations we are justified in concluding that the parathyroid glands produce a hormone which regulates the calcium exchanges of the body, and that in the absence of sufficient calcium the nervous system is unduly irritable. Tetany may occur in many clinical conditions besides disease of the parathyroids, and in some of these the calcium content of the blood is also very likely to be lowered—*e.g.*, rickets, pyloric stenosis, dilatation of the stomach, prolonged lactation.

That tetany does not more frequently follow partial removal of the thyroid is probably due to the position of the parathyroids in a part which is usually left untouched. In 1921 Sir James Berry reported that in 1,338 operations for goitre he had never had a case of tetany. But he stated that he always left a piece of gland at the hilus. Dunhill had operated on many hundreds of such cases before he had two cases of tetany. The risk is a real one.

The normal calcium content of the blood averages 10 mgm. per cent., and will be found to be distinctly lower than this in tetany. When there is a tendency to tetany it will be found that pressure on the nerves or vessels of a limb will bring on the attack (Trousseau's phenomenon), that the motor nerves are unduly excitable to galvanism (Erb's symptom) and that, when the facial nerve is lightly tapped as it crosses the jawbone, spasm of the facial muscles on that side occurs (Chovstek's sign).

Although it is generally held that calcium lack is the responsible factor, Noel Paton has pointed out that, when the parathyroids are removed, guanidine accumulates in the muscles, and he believes this to be the cause of tetany, since a similar effect is produced by the injection of guanidine. Excess of guanidine is found in the urine of patients with idiopathic tetany.

The nervous symptoms of parathyroid lack may apparently extend beyond simple tetany. Hurst in 1915 reported a case of fibrillary twitchings, tremors, restlessness, and diarrhœa, coming on two years after removal of the greater part of the thyroid, which was aggravated by thyroid extract, but greatly benefited by gr. 1/10th of parathyroid extract four times a day. Cordier has described the case of a man aged 41 who suffered from tetany and diarrhœa, among other symptoms, as a result of hæmorrhages into the right and left parathyroids. These symptoms were relieved by administration of fresh parathyroid glands, but when a second hæmorrhage occurred this treatment failed. G.H. Clark's description of three cases in children of chronic parathyroid defect has already been referred to.

Although it is not clear, as Collier says, upon which part of the neuro-muscular apparatus the morbid process is incident, it has commonly been assumed that the basal ganglia chiefly suffer from this parathyroid lack, and treatment by parathyroid extract has been recommended for diseases in which that part of the brain is involved, such as lethargic encephalitis and Parkinson's disease. Although one case of myoclonic movements following encephalitis under my care was benefited in this way, and the blood calcium was restored to normal, I have

not been much impressed with the effects of parathyroid treatment in this group of diseases.

I have come to think that parathyroid extract is useful in some cases of functional albuminuria. Almroth Wright some twenty years ago showed that the blood calcium was deficient in these cases, so that the viscosity of the blood was lowered and albuminuria occurred as a serous exudate. Functional albuminuria is apt to occur during a period of active growth, when the skeleton is making great demands for calcium salts. In one such case of rapid growth, where the albuminuria was accompanied by great irritability of the muscles and a lack of dentine in the teeth, treatment by calcium salts and parathyroid extract led to great improvement in the albuminuria and in the muscular and nervous state. It is interesting to recall that in rickets, where calcium metabolism is also impaired, nervous symptoms, such as laryngeal stridor and night terrors, are not uncommon.

Fresh interest in the parathyroids was aroused by the work of Vines and Grove, who showed that in the case of lesions that could be directly observed, such as a varicose ulcer on the leg, the calcium content of the blood could be raised to normal by giving parathyroid extract, and that this was followed by speedy healing. They then applied the method to internal lesions, such as gastric and duodenal ulcers, and claimed similar results. In two cases of chronic gastric ulcer, however, I had the blood calcium estimated, and it was found to be slightly above normal, so that the method is not of universal application. But striking benefits have been reported from this treatment in sprue, for which condition it was suggested by Harold Scott, who found the blood calcium to be low in this disease. This observation raises interesting speculations. The tongue in sprue resembles that of pernicious anæmia, and various other conditions in which achlorhydria is a feature common to all. Tetany is usually accompanied by an alkalosis. Calcium chloride is a soluble salt. It may well be that a due secretion of hydrochloric acid in the gastric juice is a necessary factor for the due assimilation of calcium salts, though not the only one. It is interesting to note that diarrhœa, the

characteristic symptom of sprue, was also a symptom of the cases of parathyroid deficiency.

Vines and Grove believe that calcium deficiency is an index of the absorption of a toxin, and that in all the diseases improved by parathyroid therapy the common factor is sepsis. Vines subsequently brought his work into an interesting relationship with the general activities of the vegetative nervous system. In the immediate response to infection the sympathetic is stimulated to play its part as a defensive mechanism, while in the process of healing, the parasympathetic, which is an anabolic agent, is called into play. The thyroid co-operates with the sympathetic and the parathyroid with the parasympathetic. The rationale of parathyroid therapy then is that it is a means of re-establishing the normal endocrine balance of the body which infection has disturbed.

A similar conclusion is reached by another path. The endocrine glands which co-operate with the sympathetic, *i.e.*, the thyroid, adrenals and pituitary, all tend to mobilise sugar into the blood, while the internal secretion of the pancreas which co-operates with the parasympathetic lowers blood sugar. If the view just stated is correct, parathyroid secretion should act in the same sense as insulin. Cammidge has found that it does activate insulin, and though so far I have not found it capable of replacing insulin, it may make a smaller dose effective. Eppinger, Falta, and Rudinger found that removal of the parathyroids one by one tended more and more to favour the onset of glycosuria, which confirms this view. It is at first sight curious that there should be excitement and apprehensiveness with an overdose of parathyroid. This would appear to be due to its stimulating effect on the antagonistic thyroid. A medical man who has a chronic amœbic dysentery took 30 grs. of calcium lactate and gr. 1/10th of parathyroid daily for twelve days for recurrent stomatitis, with great improvement in this symptom as well as in the stools and in his general condition. But after ten days his thyroid gland began to swell, and his eyes became slightly more prominent. There were no tremors, but his knee-jerks became much exaggerated. The neck remained in this state for three

or four days, and then gradually subsided again. It is, indeed, evidence as to the activity of parathyroid extract given by the mouth, that in unsuitable cases or in excessive doses it so frequently shows a harmful effect.

It is usual to give it in conjunction with calcium lactate, and it is seldom necessary to give more than gr. 1/10th in the day. A convenient form is the tablet containing gr. 1/40th of parathyroid and 5 grs. of calcium lactate.

We may conclude that the parathyroids have a structure and function distinct from and even antagonistic to the thyroid; that they are anabolic in function, leading to the building up of calcium in the blood and nervous tissues, having a sedative action on the latter, and promoting healing through the former, and that they co-operate with the internal secretion of the pancreas on the blood sugar. Like the thyroid, their secretion seems capable of being absorbed from the alimentary tract, though, no doubt, as the active principle becomes generally available, more striking results will be obtained by injection. Parathyroid extract has been used therapeutically for many conditions, but the best results appear to have been obtained in tetany, sprue, and chronic ulceration.

## CHAPTER V

## THE PITUITARY BODY

Like the adrenals, the pituitary has a double origin from glandular and nervous structures. The anterior glandular lobe is formed from an ingrowth of the pharynx, the posterior from an outgrowth of the mid-brain. The pars intermedia is really a portion of the anterior lobe, which has grown round the tip of the posterior lobe, and probably cells from it migrate into the posterior lobe during development. The hypothalamus, the portion of the brain immediately above the posterior lobe, is regarded by some authorities as the head ganglion of the sympathetic ; if this is so, it provides another interesting parallel with the adrenals, where the medulla originates from the sympathetic ganglion cells. In both cases the glandular portion is associated with growth and secondary sexual characters, while the portion of nervous origin provides the most readily identified secretion, pituitrin in one case, adrenalin in the other. But the pituitary, lying as it does in a bony cavity, is exposed to pressure in a way in which the adrenals are not. The overgrowth of one lobe, therefore, almost inevitably produces pressure effects on the other. Moreover, enlargement of a lobe may be accompanied by diminished function, as, for instance, when there is a cyst. It is not surprising, therefore, that the symptoms of pituitary disease are mixed and confusing. For a full discussion of them that admirable work of Cushing must be consulted, *The Pituitary Body and its Disorders.*

But the following main facts emerge : certain effects are due to direct pressure ; primary optic atrophy and bitemporal hemianopsia from pressure on the optic nerves ; varying degrees of ophthalmoplegia from the pressure on the third nerves as they pass through the cavernous sinus ; loss of the sense of smell from pressure

on the olfactory nerve; headache, both frontal and radiating down the back of the neck, (a "triangular" pain), and drowsiness, which may become extreme. With the somnolence there may be ravenous appetite. A skiagram may then reveal erosion of the pituitary fossa, so that its normal size of 10 by 8 mm. is exceeded, and the clinoid processes may disappear entirely or in part.

The secretion of the anterior lobe is colloidal in character; as this lobe is an outgrowth of the alimentary tract, one might expect its secretion to be absorbed by that tract, and Gardiner Hill's observations seem to show that this is the case. It appears to have an effect on body temperature, growth, the bony and cutaneous tissues, and the sexual organs. Removal or disease of this lobe leads to a subnormal temperature, and injection of its extract then causes a febrile response, a point of some diagnostic value. Moreover, anterior lobe extract, given by the mouth, has been used to raise the subnormal temperature in hypopituitarism. If this lobe be removed in young animals, the development of both primary and secondary sexual characters is much interfered with, while that infantile gland, the thymus, remains large. On the other hand, feeding with anterior lobe accelerates their growth and maturity. Mr. Crossley-Meates has kindly informed me that he gave 2 grains of anterior lobe extract daily to an Irish wolfhound bitch-pup of four months old. In a month the facial expression became heavy and the ears large, so that it resembled a blood-hound. The long bones were definitely larger and heavier than those of the rest of the litter. But the most striking difference of all was the change in character, for this bitch-pup would domineer over the rest of the litter, including the dog-pups, and at eight months old she was more masculine and rougher in play than they were.

The secretion of the posterior lobe, pituitrin, passes into the central canal of the nervous system. It is apparently not readily absorbed when given by the mouth, though some experiments by Hamill show that this can, at any rate, occasionally happen. But it can be absorbed from the nasal mucosa, as Blumgart proved, presumably because it is more closely associated with this

in development than with the alimentary tract. Nevertheless, to ensure its action, intramuscular or intravenous injection is usually required. Its action is widespread, and may be summarised thus :—

(1) It is a stimulant to plain muscle. The pulse is slowed and the blood pressure is raised. The slowing is not abolished by section of the vagi or by atropin, so that it is not centrally but peripherally produced. A repetition of the injection within half an hour or so does not repeat this effect. It causes contractions of the pregnant uterus, the intestines and the urinary bladder. All these effects are much more marked when these muscles are in an atonic condition.

(2) It is a galactogogue. This is usually explained by its action on the plain muscle of the mammary ducts. Leslie Pugh showed that an injection would prevent a cow from holding up her milk, as she may do when a strange milkman comes to her, but that the ultimate yield of milk was not increased thereby. This suggests that sympathetic inhibition of the secretion was overruled, but that no more milk was secreted than usual. Yet clinical observations recorded later would seem to show that an overacting pituitary may lead to an abnormally prolonged period of lactation.

(3) Both diuretic and antidiuretic effects have been noted. This can probably be best expressed by saying that pituitrin regulates the threshold of the kidney for the excretion of water, or in Schäfer's phrase it produces those conditions which are most favourable to renal activity. This is discussed under "diabetes insipidus."

(4) It is antagonistic to insulin in preventing a fall of blood sugar.

J. H. Burn, who first observed this (*Journ. of Physiol.*, LVII, No. 5, 1923), considered the antagonism to be a direct one, but Lawrence and Hewlett (*British Medical Journal*, May 30th, 1925) believe it to be indirect, the pituitrin mobilising the glycogen of the liver as sugar into the blood. They come to the further interesting conclusion that pituitrin seems to have a balancing action on carbohydrate metabolism, inhibiting the effect of drugs which tend to change the blood sugar concentration away from normal in either direction. This would pro-

vide a striking parallel with its effect on the excretion of water.

(5) It plays an important part in promoting the transport of fat to the liver, where it is normally metabolised. Hence the obesity of hypopituitarism. Here again insulin antagonises pituitrin (Cope). This must be one factor in the rapid increase in weight which often occurs in a patient undergoing insulin treatment.

From this brief statement it is clear that the pituitary gland plays a part in nearly all the important bodily functions.

**Affections of the Anterior Lobe.**

(1) **Overaction.** Since the anterior lobe is such an important factor in growth, it is not surprising to find a difference between its pre- and post-adolescent affections. As explained in Chapter II, during the pre-adolescent period overaction of the anterior lobe leads to gigantism or hemi-hypertrophy, while underaction is believed to be responsible for the Lorain type of infantilism. Later on, when epiphyseal junctions are completed, such general overgrowth is not possible as a result of overaction, but the condition known as *acromegaly* is produced. This is particularly likely to affect persons whose large size suggests a previous tendency to an overactive pituitary. It involves particularly the jaw and the extremities. Not only the bones, but the soft parts share in this overgrowth. Keith points out that it is just those parts which are most used that hypertrophy. He considers that the physiological hypertrophy resulting from increased use is brought about by products of metabolism stimulating the growth hormones of the pituitary; a chemical reflex action. In acromegaly the disordered condition of the pituitary leads to the flooding of the body with such hormones after most trivial muscular action; hence there is unregulated growth.

The skull resembles that of anthropoid apes and palæolithic man in the exaggeration of the bony prominences and crests. The cranial sinuses are large, as is the pituitary fossa. There is hyperplasia of the anterior lobe of the pituitary, with a tendency to secondary degenerations. The lower jaw is much enlarged, and the vertebral

column is kyphotic. The terminal phalanges are broad and thick, often with exostoses. The skin and subcutaneous tissues are thickened, and there is an overgrowth of hair. The thyroid generally undergoes enlargement, which may be cystic. Enlargement of other ductless glands is not uncommon. The external genitals are usually hypertrophied, though the gonadal glands are often degenerated. Gordon Holmes has called attention to the enlargement of the colon.

The patient notices that he requires larger hats, gloves and boots. Headache may be severe, both frontal and occipital, radiating down the back of the neck. Pains in various parts of the body, irritability, moroseness and morbid introspection are not uncommon. In women there may be amenorrhœa. The blood sugar curve tends to be raised, and glycosuria may occur. The basal metabolic rate is sometimes increased. I have seen severe recurrent intestinal hæmorrhage. Pressure effects on the second and third cranial nerves may be observed. Of late attention has been called to the association between epilepsy and acromegaly and other pituitary enlargements. Somnolence is often a marked symptom.

The course of the disease is variable; it is liable to remissions, and is compatible with prolonged life. Treatment is unsatisfactory. Small doses of thyroid extract, and iodine or potassium iodide appear to afford most relief. There do not seem to be rational grounds for giving extract of the pituitary when that gland is already overactive. Aspirin often relieves the headaches. When the headaches are very severe and the eyesight is definitely failing, the operation of decompression may be called for.

Just as the overgrowth in pre-adolescence may be general or partial, so may the post-adolescent overaction produce the general disturbance of acromegaly or a more partial one like *osteitis deformans* (Paget's disease). At least this appears to be the most probable explanation of this rare condition; certainly the pituitary fossa may be enlarged, though this is conceivably a result rather than the cause of the disease. Syphilis has also been suggested as a cause. Unlike acromegaly, osteitis deformans does

not affect the soft parts, but attacks chiefly the long bones of the lower extremities, the clavicles, and the vault of the skull. The periosteal bone is thickened, yet the whole structure is weakened, so that the bones bend. The whole appearance becomes ape-like. It chiefly affects men over 50, and does not tend to shorten life, although it may cause a good deal of pain. Treatment is of little avail; potassium iodide may help, but not to the extent that might be expected if the disease were syphilitic.

(2) **Underaction.** The only definite disease produced by pure underaction of the anterior lobe that I am prepared to recognize is the *Lorain type of infantilism*, which has been already described. In animals, partial removal of the anterior lobe leads to lack of skeletal development with undergrowth. It is possible that various menstrual disorders may be due to this cause in adult life, but no clear-cut clinical picture is produced thereby. Gardiner Hill has shown that defective action of the anterior lobe produces a raised blood sugar curve, which can be lowered by feeding with this lobe. As we shall see, there appears to be an antagonism between the two lobes in this respect.

**Affections of the Posterior Lobe.**

(1) **Overaction.** The principal symptom of overaction of the posterior lobe is *glycosuria*. This is the result of the direct antagonism between pituitrin and insulin.

According to Mackenzie Wallis, the sugar curve is unduly raised and rounded in form, falling too slowly. It is interesting that he finds the glycosuria of pregnancy gives a very similar curve, in view of the effect of pregnancy upon the pituitary.

The true nature of pituitary glycosuria is not likely to be recognised unless there are concomitant signs of overaction of the anterior lobe. Thus I saw a woman of 42 with glycosuria who looked acromegalic. She had whiskers, and her blood pressure was 170 mm. X-ray examination showed an enlarged pituitary fossa. She proved to be pregnant and subsequently developed hydramnios. The sugar at first yielded to treatment, but became less amenable as the pregnancy advanced.

The hydramnios is interesting, as it is a common complication of pregnancy in true diabetes. Yet pregnancy must be rare in diabetics of 42. She was delivered of a living child, and remained free from sugar on an ordinary diet for about two years, after which she became apparently a typical diabetic. This case is interesting because it shows features common to pituitary glycosuria and true diabetes. Presumably her pregnancy stimulated a pituitary already tending to be too active, and during this extra stimulation her blood sugar was sufficiently raised to excite glycosuria. On becoming free from glycosuria after delivery she neglected to diet, and thus kept her blood sugar at a sufficiently high level to damage the cell islets of her pancreas, ultimately producing ordinary diabetes.

Geoffrey Evans and Mackenzie Wallis have called attention to a form of intermittent glycosuria, apparently of pituitary origin. The pituitary plays a considerable part in rhythmical functions, witness its association with menstruation; and this form of glycosuria sometimes appears to be cyclical. I had one of these cases under observation in hospital for six weeks in 1919, and only found sugar in the urine on two occasions, even though the diet was unrestricted during part of his stay, and then in very small amounts. There may be polyuria even when there is no glycosuria. The fingers are apt to be square-ended like those of an acromegalic. It is noteworthy that in one of their cases Evans and Mackenzie Wallis found a low blood sugar curve, and this suggests that so-called intermittent renal glycosuria may be of this type. Their other case showed an undue rise in the curve during the phase of glycosuria and a normal curve during the phase of apparent quiescence. In a somewhat similar case, reported by Mackenzie Wallis and Roper, the phase of glycosuria was accompanied by acetonuria. This may be due, as pointed out by Maclean, to the loss of carbohydrate being sufficient to cause a starvation acetonuria, the available carbohydrate in the blood being inadequate to allow of complete oxidation of fats.

Such cases do not appear to deteriorate as a rule. A boy of not quite thirteen was admitted to St. Bartholomew's Hospital in July, 1925, with a history that seven

weeks before he had thirst, polyuria and boils. Glycosuria had been found, but cleared up with alimentary rest. It returned a month later, but soon disappeared again. A brother had died of diabetes at the age of fourteen. He was remarkably mature for his age, looking at least sixteen ; well-developed sexually and with a good deal of hair on his legs. His blood sugar was 0·06%, and there was no glycosuria on admission. There was always polyuria, sometimes reaching 3,000 cc., but no glycosuria during his fortnight's stay in hospital. The sugar curve showed a rise to 0·233 at the end of an hour, remaining at 0·217 after 1½ hours ; yet there was no glycosuria after 50 grammes of dextrose. His pituitary fossa was normal. He kept free from sugar, although taking 70 grammes of carbohydrate a day until January 20th, 1926, when there was some return, which quickly cleared up after a fast. On a diet containing 48 grammes of carbohydrate there was no return of glycosuria, but his blood sugar stood at 0·185% 3½ hours after breakfast. Yet a week after re admission his blood sugar curve was quite low, and there was no glycosuria after 50 grammes of dextrose. The epiphyses of the humerus and the olecrana had already united, three and seven years respectively too soon. An exostosis previously noted on his right femur was larger, and there was rarefaction in several bones, which in the shaft of his left radius amounted to cavitation.

Although his pituitary fossa was normal, a pituitary disturbance was suggested by his premature development, the early bony unions and the dystrophic condition of some bones, as well as by the polyuria when the glycosuria was absent. The glycosuria was quite intermittent and did not correspond at all closely to the diet ; and the blood sugar was too low at one time and too high at another. I think he can fairly be considered as one of the rare cases of intermittent glycosuria of pituitary origin.

**(2) Underaction.**

(a) *Diabetes Insipidus.* It is clear that several different conditions have been thus described. Erich Meyer in 1905 described a type dependent on a primary defect

in the kidneys rendering them incapable of secreting urine of a normal concentration, so that a much larger amount of water is needed to remove the ordinary products of metabolism. He found that 20 grammes of sodium chloride would cause a marked diuresis, whereas the normal kidney would respond by secreting a more concentrated urine. Yet in spite of diuresis the excretion of the salt would be incomplete even for days. He also showed that theocin sodium acetate, which increases the permeability of the kidney and is normally a diuretic, does not act as such in these cases, because in facilitating the excretion of solids it does away with the necessity for such dilute urine. Personally I should not regard these cases as diabetes insipidus at all, but as allied to interstitial nephritis. Indeed, the clinical termination in uræmia and the post-mortem findings in some cases diagnosed as diabetes insipidus strongly support this view. In cases of Meyer's type I agree that theocin sodium acetate has no diuretic effect, though it has in true diabetes insipidus. Rabinowitch has shown that in ordinary diabetes insipidus, unlike chronic interstitial nephritis, the power of concentration is quite good for nitrogen, which confirms the distinction I am drawing. It follows that restriction of the intake of fluids is a futile and cruel procedure in this renal type of polyuria, since the kidney cannot deal with a concentrated solution.

It is well known that syphilitic meningitis at the base of the brain can produce the symptoms of diabetes insipidus, especially in children. The Wassermann test is, therefore, imperative in every case, even when there are no stigmata of syphilis, congenital or acquired. The nearer the meningitis is to the interpeduncular space, the more apt it is to excite diabetes insipidus. The fact that some of these patients remain fat also suggests a pituitary defect. Obvious disease of the pituitary body may certainly be associated with persistent polyuria. The association of pituitary tumours with diabetes insipidus has been recognised since 1882. In 1912 Frank collected 85 cases of bitemporal hemianopsia, in 18 of which there was diabetes insipidus. Fractures of the base of the skull often excite a transient glycosuria, and may induce a more prolonged polyuria, presumably by damage to this region.

In other cases of diabetes insipidus there may be no evidence of syphilitic meningitis, pituitary disease or renal incapacity. The polyuria is then sometimes regarded as secondary to polydipsia. But if so, it ought to be possible to reduce the output to normal, even at the cost of much discomfort to the patient. This is not what occurs, for a point will be reached at which further reduction of intake will not be followed by a fall in output. In such cases valerian will diminish both thirst and polyuria. This can be proved by direct observation, and we should not be deterred from the use of this drug because it has sometimes been used irrationally or because absurd explanations were formerly given of its mode of action.

The three types of diabetes insipidus due to syphilitic meningitis, frank pituitary disease, and the so-called primary form, show remarkable resemblances to one another, and a sharp contrast with the renal type. It is, therefore, reasonable to suspect a common cause for them and to look for it in the pituitary. It is tempting to assume that even in the primary type there is some nervous or toxic disturbance of the pituitary, when we know that drugs such as valerian, codein and pituitrin may help all three forms. This is further suggested by the fact that the carbohydrate tolerance is raised in diabetes insipidus, and can be lowered by pituitrin injections (Lawrence and Hewlett).

The diuretic effect of pituitrin described by Schäfer and Magnus in 1901 is quite transitory. Indeed, most of the earlier experiments must be discarded, because allowance was not made for the complications introduced by anæsthetics. Farini in 1913 was the first to show that injections of pituitrin diminished polyuria.

Several observers, such as Bailey and Bremer, maintain that it is not the posterior lobe of the pituitary itself which is at fault, but the nervous tissues of the hypothalamus and tuber cinereum. Indeed, they regard the hypothalamus as the head ganglion of the sympathetic nervous system. It would be extraordinary in that case for an anti-diuretic hormone to be produced in close anatomical relation to the hypothalamus if it had no physiological relation with it. If we inquire at what

point pituitrin normally acts in its control over diuresis, we find, firstly, that it does not interfere with absorption of water from the bowel, since it does not provoke diarrhœa, as it would do if large quantities of water remained there, particularly as pituitrin provokes peristalsis. Secondly, it does not act through the vasomotor system, since it is equally effective on the denervated kidney, and no obvious effect on the renal circulation was noted by Priestley. Indeed, Priestley's experiments, in which an injection of pituitrin delayed diuresis by four to six hours, during which time the ingested water was stored up in the tissues, while dyes could still be excreted in a concentrated form, point to some direct inhibitory action on the renal tissues. Œhme considers that pituitrin inhibits the sensitiveness of the kidney to hydræmic stimulus. I should agree with Rabinowitch that diabetes insipidus is due to the lack of some internal secretion which normally regulates and moderates diuresis by acting on the cells of the kidney, and I look upon pituitrin as that secretion. We can express the situation more concisely by saying that *pituitrin regulates the threshold of the kidney for water.* This would account for the apparently aberrant instances of a diuretic effect of pituitrin. It would also explain its selective action on water while not hindering the output, for instance, of dyes. If the hypothalamus is responsible, we must, at any rate, admit that it acts through the posterior lobe of the pituitary, and not through the vasomotor system. This would offer an interesting parallel with the adrenals, where the medulla is formed from sympathetic ganglion cells, but secretes a chemically active substance. The posterior lobe of the pituitary is an outgrowth of the central nervous system in the neighbourhood of the hypothalamus, and certainly forms a chemically active secretion. The fact that diabetes insipidus may follow lethargic encephalitis, in which other signs of mid-brain lesions are present, seems to show that hypothalamic lesions may excite polyuria, but I would suggest that they operate by depriving the pituitary of its normal nervous stimuli.

Even then some facts remain to be explained. Why should lumbar puncture have such a striking effect for

a time in diabetes insipidus? Would the mere withdrawal of only 5 cc. of cerebrospinal fluid relieve pressure on the hypothalamus or pituitary so effectively as this? Why, since pituitrin passes into the cerebrospinal fluid, cannot an oliguric substance be found there, although an oxytocic substance can? Evidently there is need for further observations on such points.

Naturally the cause of any case of diabetes insipidus must be treated as far as possible; for instance, by antisyphilitic remedies when the Wassermann reaction is positive. But nothing relieves symptoms so well as intramuscular injections of pituitrin. It may be found that while $\frac{1}{2}$ cc. has no effect, 1 cc. will check polyuria for 16 hours. Since Blumgart suggested intranasal spraying with a solution of pituitrin of half strength, or the introduction high up into the nostrils of pledgets of cotton-wool dipped in the same solution, I have used this plan with some success. In one case striking benefit was derived from nasal plugs; $\frac{1}{2}$ cc. being inserted into one nostril on rising, $\frac{1}{4}$ cc. into the other in the afternoon, and $\frac{1}{4}$ cc. on going to bed. In this way the patient was kept in comfort throughout the 24 hours.

The sinister prognosis formerly attached to diabetes insipidus must have been based on the cases of pituitary tumour, or those which were really chronic interstitial nephritis. In the other cases the prognosis as to life is not so bad, although the polyuria is persistent.

(b) *Pituitary Obesity.*

Since pituitrin is a chemical entity which has a demonstrable effect in controlling diuresis and on fat transport, it might be expected that when it is in defect both polyuria and obesity would result. But though this occasionally happens, it is not the rule, which is difficult to explain. The fully developed picture of Fröhlich's syndrome will be referred to later, as probably both lobes are involved in this. But just as overaction of the anterior lobe may have general or local effects, so underaction of the posterior lobe may lead to general obesity or localised fatty deposits. Of the latter type, Dercum's disease—adiposis dolorosa—is a good example. But even here

there is sometimes genital hypoplasia, showing that the anterior lobe is also implicated. Tumours or other lesions of the pituitary have been found, and there are usually lesions in the thyroid as well. The disease begins as a rule insidiously with the appearance of fatty tumours or diffuse deposits of fat. It is much commoner in women, and usually in those who are already stout. The swellings are decidedly painful, and the skin over them may be reddened. The neighbouring nerve cords are also tender. It is interesting to note that the face, hands and feet escape, while they are affected most in acromegaly. There is marked asthenia, and trophic ulcers sometimes develop. Various organic diseases of the nervous system may complicate the condition; thus I have seen disseminate sclerosis come on quite rapidly. Psychic changes are common, irritability and depression being the commonest. From these obvious signs of nervous damage it is probable that the hypothalamus is involved, as well as the pituitary gland. The disease is refractory in treatment, but I have seen decided benefit from thyroid extract together with injections of pituitrin, especially when combined with a suitable diet for obesity. I do not think diet has any effect except when combined with such organotherapeutical measures. Aspirin may relieve the pain, and if the Wassermann reaction is positive, mercury and iodide are indicated.

**Fröhlich's Syndrome.**

In this form of hypopituitarism both lobes appear to be involved, as indicated by the genital infantilism and the obesity. Brissaud's type of infantilism seems to be the same syndrome occurring in childhood.

Gardiner Hill finds that about one-third of the cases of pituitary obesity show an onset at birth. But in the others he finds there is usually a stage of hyperpituitarism, which is followed by exhaustion of the gland, as stated by Cushing, and as I have repeatedly observed. This is shown in the early fusion of the epiphyses, the assumption of adult proportions, and onset of catamenia. Recently I saw in one week three cases of Fröhlich's syndrome, in which the catamenia had started between 9 and 10, subsequently ceasing as the hypopituitarism developed.

Again, the bones in a Fröhlich are generally unduly solid, pointing to a previous overactivity of the anterior lobe. In some of the cases there is a history of an acute specific fever just before the onset of obesity. Indeed, the putting on of weight after fevers, especially after typhoid, which is so often taken as a good sign, is more probably due to exhaustion of the pituitary or thyroid. This may be temporary, but I have seen permanent and gross obesity after typhoid fever.

I have already referred to the rounded face with clear skin and good colour which characterises the Fröhlich. The fat tends to accumulate round the limb girdles, extending down to the elbows and knees; in the lower extremities the fat may hang over the knees, which I have called the "plus fours" distribution. The ankles are usually thick, but the hands and feet are often quite slender. There are rolls of fat round the back, spreading forwards into and below the breasts. In the male the fat is apt to follow a feminine distribution on the breast and mons, while in the female the breasts may be very pendulous, though sometimes they are poorly developed, most of the fat being submammary. The skin on the back of the upper arms and outer aspect of the shins is reddened. They bruise very easily, possibly due to the polycythæmia which is usually present. This last feature is not a consequence of the amenorrhœa, since it is found in male Fröhlichs. Parkes Weber has called attention to the large cutaneous striæ which are often present. In 60% the pituitary fossa is definitely reduced in size, and the entrance to it is narrowed by the approximation of the clinoid processes. The patients are not necessarily short in stature; Gardiner Hill finds the younger ones are generally taller than the average, pointing again to preliminary hyperpituitarism, but the older ones are either of average height or below it. The hair on the body is scanty and feminine in distribution, and in men the beard does not grow. Recently I have seen cases which strongly suggest that in the alopecia referred by dematologists to nervous causes the pituitary may be the intermediate mechanism through which the primary cause operates.

Genital hypoplasia is the rule, but not invariable. In

males the external genitals are infantile, and the testes may be undescended. In women there is generally an infantile condition of the internal generative organs or some gross defect of them, while the breasts, despite their size, contain little glandular tissue. Amenorrhœa is the rule. But the very important relationships between the pituitary and the reproductive organs will be discussed in another chapter.

The basal metabolic rate is lowered in 68% (Gardiner Hill), but this may be partly due to coincident changes in the thyroid.

The blood sugar curve rises too high and falls too slowly in the early stage, here again suggesting hyperpituitarism. In the later stages it is too low, and then there is increased sugar tolerance. This must be due to increased storage, since giving carbohydrates to such patients does not raise their respiratory quotient as it does in normal individuals. Since pituitrin and insulin are antagonistic, this is probably due to the unopposed action of insulin, sugar being readily converted into and stored as fat. As pituitrin helps in the transport of fat to the liver for metabolism there, a deficiency in its supply would also tend to increase obesity directly. I have already referred to the somnolence in some of these patients. The fat boy in Pickwick, "Drat that boy, he's asleep again," is usually quoted as a classical example. A few years ago a very fat Jew, weighing 20 stone, turned up at St. Bartholomew's Hospital at 11 p.m. complaining that he felt very sleepy. Fortunately he had a doctor's card with him, otherwise I cannot help thinking a fat Jew complaining of sleepiness at 11 o'clock at night might have received more advice than treatment. It was a good thing he was admitted, for he had a syncopal attack soon afterwards. X-ray examination showed enlargement of his pituitary fossa. Under injections of $\frac{1}{2}$ cc. of pituitrin, three times a day, he lost two stone in 10 days, and his general condition improved remarkably. More recently I advised two daily doses of $\frac{1}{2}$ cc. in a similar case, with the result that $17\frac{1}{2}$ lb. were lost in twelve days. In yet another case, 1 cc. of pituitrin daily was followed by the loss of 13 lb. in fifteen days.

This tendency to syncopal attacks must not be

forgotten in cases of pituitary obesity. Presumably it is due to fatty infiltration of the myocardium. Unfortunately it is sometimes combined with a considerable rise in blood pressure, to which the obese are prone, which increases the load on a feeble heart, and may precipitate a fatal attack of myocardial failure. But apart from this the prognosis as to life is not bad.

**Treatment.**

The best results are obtained by the combined use of thyroid and pituitary extracts. Gardiner Hill's observations conclusively prove that this combination is more effective than giving either gland separately. He gives ½ gr. of thyroideum siccum and ½ gr. of pituitary, whole gland, extract every night, increasing until 5 or more grains of each are given three times a day, until a definite effect is produced on metabolism and obesity. It need hardly be said that such large doses would require careful watching; I should not care to give them unless the patient were in hospital or a nursing home. He then suspends treatment for a month or more, but as soon as the weight begins to go up again he resumes it, though with smaller doses. Gradually the intervals can be prolonged and the doses lessened. Both the basal metabolic rate and the blood sugar curves of either variety become more normal, while the catamenia return or become more regular.

*Note*.—While these pages have been passing through the Press Cushing has adduced evidence to show that while the growth factor is dependent on the anterior lobe, the obesity factor, like that responsible for diabetis insipidus, resides in the hypothalamus.

## CHAPTER VI

# THE ADRENALS AND THE CHROMAFFIN SYSTEM

### THE ADRENALS.

The adrenals, although discovered in 1564, were not known to have any function until the classical work of Addison in 1855. Like the pituitary, they are of double origin, the cortex developing from the Wolffian body, while the medulla arises from the sympathetic nervous system. Swale Vincent has shown that in fishes these two parts form separate structures, the cortex being represented by a median inter-renal body, the medulla by the chromaffin bodies or paired suprarenals. Higher in the vertebral scale than the fishes the two portions come together, and if this fails to occur, the central nervous system fails to develop beyond the fish-stage, resulting in anencephaly. But even after this fusion chromaffin bodies are still found in association with sympathetic ganglia, and occasionally accessory cortical glands also occur. When in evolution the sympathetic cells emigrated from the central nervous system into outlying ganglia, they were accompanied by these chromaffin cells, but as the sympathetic nervous system becomes more developed, the chromaffin cells become more restricted, until in the higher animals they are mainly confined to the adrenal medulla. This explains why preganglionic sympathetic fibres end in the adrenal gland, whereas in every other instance they end in synapses round sympathetic ganglion cells, from which the post-ganglionic fibres proceed.

In the case of the adrenals the medullary cells *are* the sympathetic ganglion cells, and we have here another interesting example of a nervous structure assuming secretory properties. It is of striking interest to find, as Langley showed, that their secretion, adrenalin, has the

same effect on any part as the stimulation of the sympathetic nerves to that part.

The earlier experiments on the adrenals showed that they were essential to life. In 1895 Schäfer and Oliver proved that an extract from them raised blood pressure, and before long it was shown that it was only the medullary extract which was responsible for this. In 1901 Takamine prepared the active principle in a crystalline form, called it adrenalin and showed it contained a benzene ring. Soon after this it was imitated synthetically. According to Biedl 4·3 mgm. are produced in 24 hours. Besides raising blood pressure by its constrictor effect on the vessels, it stimulates the force and frequency of the heart beats, actually dilating the coronary vessels in spite of this general constrictor effect. If the blood pressure rises too high, however, the cardio-inhibitory centre is stimulated, over-riding this augmentor effect. Like the sympathetic, it checks peristalsis in the stomach, while causing the pyloric sphincter to contract. It acts in the same way on the gall bladder and its sphincters, on the small intestine and the ileo-cæcal valve, the colon and the anal sphincter, the urinary bladder and its sphincter. As pointed out by T. R. Elliott, the law of the hollow viscus is that, since this simultaneous inhibition of peristalsis and closure of the associated sphincter facilitates "the quiet lodgment of contents," both actions are carried out by the same nervous mechanism. Its effect on the uterus is variable, according to the muscle fibres affected. According to Langley, it relaxes the cardiac sphincter, and it certainly relaxes the bronchial muscles. It can cause diuresis secondarily to the raised blood pressure, and in large doses it may produce salivation and sweating.

In all these respects it appears to sensitise the neuromuscular junction to sympathetic stimulation. According to Elliott, in the absence of adrenalin, excitation of sympathetic nerves produces very little effect. Adrenalin, therefore, seems to play an important part in activating the defensive mechanisms of the body, for which the sympathetic is responsible. It raises blood sugar and may excite glycosuria because it acts on the liver in a contrary sense to insulin, tending to empty its glycogen

reservoirs. It also leads to fatty changes in the liver.

It is somewhat surprising, in view of the identical effects produced by injection of adrenalin and stimulation of the sympathetic, to find that Stewart and Rogoff's careful series of experiments leads them to conclude that adrenalin is steadily secreted under nervous action controlled from a spinal centre, which is not specially brought into play by emotional stresses and physical strains, and that it is not essential to the organism. In effect, they deny the whole theory of the emergency action of adrenalin. These conclusions are so diametrically opposed to those of other workers that it is best simply to state them, merely adding that Cannon's recent work seems to answer many of their objections.

An extract of the cortex yields cholin, lipoids, and oxydases, but we cannot connect this with the recognised functions of the cortex.

### DISEASES OF THE ADRENAL MEDULLA.

**Overaction.** It has been claimed that excessive action of the adrenal medulla plays an important part in producing arterial hypertension. Vaquez believes that in this condition there is generally hypertrophy of the medulla. It is tempting to conclude that the cases of raised blood pressure with glycosuria in later life are due to this, since they may be induced by overstrain and worry, which irritate the sympathetic, and adrenalin excess would raise both the pressure and the sugar of the blood. But we have no conclusive evidence of this. Some cases of temporary glycosuria in such persons present the blood sugar curve termed the " lag-curve " by MacLean, and I am inclined to believe this may sometimes be due to overaction of the adrenal medulla.

**Underaction.** The classical example of this is *Addison's disease,* which is characterized by pigmentation, low blood pressure, profound asthenia and vomiting. The old controversy as to whether the adrenals or the sympathetic nervous system were responsible is solved now that we know the adrenal medulla arises from the sympathetic. The adrenal lesion is usually tuberculous, of the caseous variety, but simple fibrosis or atrophy may also be responsible, on the other hand. At St. Bartholo-

mew's Hospital, during thirteen years, four examples of caseation of both adrenals were discovered post-mortem, which had led to no symptoms during life. Presumably other chromaffin material in the body had been sufficient to carry on the functions of the adrenals. Malignant disease or syphilis of the gland may occasionally cause the disease, and one of Addison's original cases was due to the pressure of a malignant growth on the adrenal vein.

It is a rare disease ; it affects males more than females, and seldom occurs before 15.

The pigmentation chiefly affects (i) the buccal mucous membrane, (ii) parts normally pigmented, (iii) parts exposed to light or pressure. Addison described the pigmentation as " dingy or smoky," either in patches or so universally distributed that " but for the features, the patient might have been mistaken for a mulatto." I am inclined to accept Rendle Short's view that this pigmentation is secondary to the relaxation of the blood vessels, due to diminished vaso-constriction, such as occurs over an area repeatedly poulticed or exposed to increased light, heat or irritation. The pigmented epidermal cells of the water toad are known to produce a pressor amine, and more recently a similar substance has been isolated from the pigmented areas of skin in hypoadrenalism. This is suggestive of a compensatory mechanism. I have certainly noted a rapid increase of slightly raised pigmented areas on the abdomen in asthenic states, but Dr. T. H. G. Shore was unable to find adrenalin in one such area removed under local anæsthesia from a case of mine.

There is another possible explanation of the pigmentation. Adrenalin is closely related chemically to tyrosin, which is a chromogenic substance. If the adrenals are unable to convert tyrosin into adrenalin, the tyrosin might give rise to a pigmented substance. But the distribution of the pigmentation is in favour of Rendle Short's view.

The low blood pressure can be explained by the absence of normal vaso-motor tone, which is maintained through the sympathetic. It is highly characteristic of Addison's disease, and in doubtful cases of pigmentation this may settle the diagnosis. A raised blood pressure excludes Addison's disease. The pressure falls as the disease

advances; it seldom reaches 100 mm. systolic by the time the symptoms are marked; 80 mm. is a not uncommon reading, and I have found a systolic reading even as low as 60 mm. But life cannot long be maintained at that level. The diastolic pressure does not fall so quickly, so that the pulse pressure becomes very small; perhaps only 18 mm., an observation which is consistent with the brown atrophy of the heart which often occurs in this disease. The pulse is small, soft, and generally slightly increased in frequency.

There is usually dyspepsia, and sooner or later vomiting sets in. As the sympathetic supplies the stomach with inhibitory fibres, loss of their function must lead to motor irritability, and therefore to vomiting. Examination of the gastric contents does not show much alteration until near the end, when both pepsin and hydrochloric acid are reduced, as might be expected.

Asthenia is very marked, and Lombard demonstrated with the ergograph that the weakness of the voluntary muscles far exceeded that which occurred in other tuberculous lesions. This is interesting in view of the recent and still unsettled controversy as to sympathetic control over muscular tone.

Carbohydrate tolerance has been found to be raised, and the blood sugar is generally low, as might be expected. There is no characteristic change in the urine.

The outlook is very grave, but I have seen two apparent recoveries. One was in a girl of 20, whose blood pressure rose again to 120, and who regained her strength. She remained deeply pigmented, however, much to her chagrin. The other patient, a tall, weedy youth, after one or two relapses, appeared to get well, and his pigmentation was much diminished. Presumably these were cases of fibrosis and not of tuberculous disease. Byron Bramwell has suggested that X-ray examination would enable tuberculous deposits in the adrenals to be detected. Dock states that, apart from the acute cases, the duration of life is from one to three or four years, but in my experience it is much shorter than this.

This is not the place to discuss differential diagnosis, but I may say that I lay great stress on pigmentation

inside the mouth, which is rarely seen in other pigmentary diseases, and on the low blood pressure.

Treatment by adrenal extract or by adrenalin has been disappointing. Fresh glands, raw or lightly cooked, have been given. Adrenal extract in doses of from 5 to 20 grains three times a day should be tried. It is difficult to ensure absorption of adrenalin given by the mouth, but this is claimed to occur in Addison's disease, presumably because it cannot in that case prevent its own absorption by vaso-constriction in the stomach. But even then, if it began to produce improvement, the power of vaso-constriction would return, and the treatment would defeat itself. Still the drug may be given a trial, since some have reported favourably of the effects of a dose of 5 minims of the 1 in 1,000 solution, increased up to 30 minims, three times a day. If hypodermic injections of adrenalin are to be given, caution must be used, and a dose of 10 minims should not be exceeded. Leyton claims that if 3 grains of adrenal extract are given three times a day for 3 days, and the blood pressure is raised by more than 10%, the patient is suffering from Addison's disease; but I have not been able to confirm this, as the test has failed in cases where the diagnosis has been confirmed by necropsy. Transplantation of an adrenal into the testes has been carried out by Tanner in a case of Hurst's with striking improvement. Yet curiously it proved not to be a case of Addison's disease. It shows, however, that such a procedure is feasible, and might be tried.

It has been suggested that there are minor degrees of hypoadrenalism, characterised by lack of vascular tone, vasomotor instability, and low blood pressure. This is possible, since we can realise the strain which is thrown on the sympathetic-adrenalin apparatus in responding to prolonged mental and physical strain or to infections. Indeed, Elliott and Tuckett have shown the lack of chromaffin substance in the adrenals of fatal cases of diphtheria.

Sergent in 1917 called attention to the "white line" as a test for the recognition of such minor degrees of hypoadrenalism. This line is a blanching of the skin following light stroking by a blunt object. The abdomen

should be exposed for 20 minutes before the test is applied ; a pure white band should appear in 10 seconds, and last for 3 to 15 minutes. But this test is of doubtful value, as it may occur in normal subjects, or in patients after injection of adrenalin, and is specially well seen in scarlet fever.

Hæmorrhage into the adrenals has already been referred to in Chapter II. It usually occurs in infants, but I have seen one case in an adult, who died of meningococcal septicæmia, with the usual symptoms of rapid collapse.

### DISEASES OF THE ADRENAL CORTEX.

The cortex of the adrenal is believed to be more essential to life than the medulla, yet no active principle has been extracted from it. Its cells have a striking resemblance to those of the corpus luteum, and it is relatively very large in the human embryo, a fact which has been connected with the highly-developed brain of man, since the adrenal cortex and the cerebral hemispheres appear to be interdependent. Three functions have been attributed to the cortex, but there is very little evidence of two of these—a possibly detoxicating action, and a share in the elaboration of the medullary secretion. The third function, of stimulating growth and development, especially of the reproductive organs, is supported by much better evidence, chiefly clinical in character.

**Overaction.** Growth of the adrenal cortex may be associated with striking changes in the sexual apparatus, taking the form of precocious development in children, always in the direction of *virilism*, while in adult women the virilism is also marked. Presumably it is the degree of overgrowth of cells having normal cortical structure which determines whether or not an adrenal growth has this effect on the secondary sexual characters. But this subject can most conveniently be discussed under the general heading of the influence of the endocrine system on sex.

**Underaction.** *Progeria*—the premature senility of children described by Hastings Gilford is the only condition which has been associated with defect of the adrenal cortex (*see* p. 23).

### THE CAROTID AND COCCYGEAL BODIES.

The Carotid body is situated within the angle of bifurcation of the common carotid artery into its internal and external branches. It is developed from the embryonic cells of the intercarotid sympathetic plexus. It belongs to the chromaffin system such as is found in connection with other sympathetic ganglia, and can therefore act as an accessory adrenal medulla.

The Coccygeal body is immediately in front of the apex of the coccyx ; it is sometimes divided up into a number of smaller bodies. It contains no chromaffin cells, and there is no evidence that it forms an internal secretion. Rather is it connected with the vascular system, and it is probably an isolated portion of the reticulo-endothelial tissue.

## CHAPTER VII

# THE RETARDING GLANDS

The chief function of the thymus and pineal body is usually regarded as retarding sexual maturity in the interests of more prolonged somatic development. In neither case is there satisfactory evidence of the formation of an internal secretion, but they appear able to influence the endocrine balance, and that is the justification for considering them here.

### THE THYMUS.

The thymus arises from a pair of diverticula from the dorsal aspect of the third pair of gill clefts, which become surrounded by lymphoid tissue. The epithelial lining of these diverticula gradually atrophy until at birth they are merely represented by Hassall's concentric corpuscles in the medulla of the gland, where there are also many eosinophil cells. All the rest is now lymphoid tissue. The gland reaches its fullest development at the end of two years, when it begins to atrophy gradually until puberty, after which it disappears more quickly, being represented in the adult chiefly by fibrous tissue and fat, in which a few nodules of lymphoid tissue persist together with some Hassall's corpuscles. Excision of the thymus in young dogs results in obesity and cachexia, and children have developed rickets after that operation. But the most definite results of animal experiment are those recorded by Paton with Henderson and Goodall, who found that removal of the thymus hastened sexual maturity, while castration led to persistence of the thymus. This would justify the usually-accepted opinion that the thymus has a retarding action, prolonging the infantile stage, and is antagonistic to sexual development.

Although Basch laid emphasis on the epithelial tissue

in the thymus, and regarded this as forming an internal secretion, this view is not widely held to-day, the gland being usually regarded as a lymphoid structure belonging to the hæmopoietic system.

The physiological effects produced by the juice expressed from it can be explained as merely due to the nucleo-protein such a cellular structure would naturally yield, and throw no light on the functions of the gland.

In anencephaly the thymus may be either larger or smaller than normal, while in cretinism it is usually quite small. Accessory thymic nodules may be found near the thyroid, while thyroid tissue is occasionally present in the thymus. In interesting contrast with its hypoplasia in cretinism is its enlargement in Graves' disease, and I have seen extraordinarily large Hassall corpuscles in this condition. The liability of this enlarged thymus to acute congestion after operations on the thyroid should be remembered as an additional risk in this procedure. The thymus is also usually enlarged in Addison's disease and in myasthenia gravis. Petechial hæmorrhages may be seen in the gland in fatal cases of bronchopneumonia, but this is apparently merely due to the asphyxia, as it occurs in any form of death by suffocation.

Thymic atrophy constantly occurs in marasmus, in which the spleen and other lymphoid structures share. This is only occasionally seen in other wasting conditions such as tuberculosis. Dock has therefore advised thymus feeding, or, less hopefully in my opinion, thymic extract in obscure infantile marasmus.

Enlargement of the thymus is of much greater importance and interest owing to its association with congenital and infantile stridor, asthma and sudden death.

The most significant increase in the thymus is in its thickness, because this can affect the lumen of the superior aperture of the thorax. Leonard Williams points out that a child, unlike an adult, often prefers to sleep on its face. He thinks this is to diminish pressure of the gland on the trachea, and that in anyone over the age of seven such a habit indicates an enlarged persistent thymus.

Apart from the causes already mentioned, enlargement is usually part of a general hypertrophy of the lymphoid

tissue throughout the body, constituting *status lymphaticus*. This is important, because adenoids and enlarged tonsils may call for removal, and if they are part of a status lymphaticus, there is an added risk in the anæsthetic. This enlargement of the thymus is a true hyperplasia of its lymphoid tissue.

The sufferer from status lymphaticus is usually fat and pasty, and may show signs of infantilism. He may be liable to attacks of *stridor*, especially after a screaming fit, or when the head is thrown backwards. When the stridor is severe there is retraction of the chest on inspiration. In thymic *asthma*, there is paroxysmal dyspnœa with inspiratory stridor ; the face is at first cyanotic and then pale, the pupils are dilated, the arms extended and the hands clenched. The heart sounds become feeble, and the child may die unless the attack subsides. The recovery after an attack passes off is very rapid. Unfortunately, attacks tend to recur, and ultimately to prove fatal, though I have seen patients outgrow the condition. I have seen a case in a girl aged 17.

Sudden death may occur in status lymphaticus without preliminary dyspnœa. Some cases attributed to " overlaying " are probably in reality usually this. Sudden death in the early stages of anæsthesia (when it may be preceded by a slight tetanic convulsion), during bathing, or after an injection of serum, are generally due to this cause.

Four explanations have been given of this tragic event.

1. **Intravascular Clotting.** An extract of the thymus will certainly produce intravascular clotting and therefore sudden death, but this does not represent a normal secretion of the thymus, and simply owes its effect to the thrombokinase it contains. Moreover, although thrombosis of the internal jugular vein is sometimes found, as a rule intravascular clotting is absent in cases of thymic death. This explanation may, therefore, be dismissed.

2. **Pressure on the Trachea or the Vagus.** Flattening of the trachea has been observed post-mortem, and relief of dyspnœa has followed raising of the gland from the trachea by operation. Moreover, petechial hæmorrhages are found, as in other deaths by asphyxia. But the death is too sudden to be entirely due to asphyxia. The right

ventricle may be found compressed, and the left dilated, while there is probably œdema of the lungs. There is, therefore, presumably a cardiac factor, and this may be due to pressure on the vagus, inhibiting the heart.

**3. Toxæmia.** The general lymphatic hypertrophy suggests that the body has been reacting to some infective process. On this view the death is merely the terminal event of intoxication. Its association with diphtheria is cited as in favour of this view. The toxin is presumed to act on the respiratory and cardio-inhibitory centres in the medulla.

**4. Anaphylaxis.** The cases in which an injection of serum has caused sudden death are quoted in support of this view. There seems to be a vagotonic element in the cardiac failure, and in vagotonia there is an abnormal sensitiveness to foreign proteins. Such individuals stand ordinary infections badly; this provides a link between this and the third cause. On the whole, mechanical pressure seems to be the chief factor, but the fatality could hardly be so sudden were it not for some other influence, which I should consider to be anaphylactic or allergic.

In view of the seriousness of status lymphaticus it is important to enquire whether the condition can be recognised during life. Pasty obesity is not always present, nor is it in itself sufficiently diagnostic. Occasionally the upper part of the sternum may be protuberant, and the enlarged thymus may appear above the sternum when the head is thrown back; but these signs are not common. On percussion there may be an area of dullness in the form of an inverted triangle with its apex truncated, starting behind the clavicles and merging into the cardiac dullness below. It, therefore, resembles the dullness produced by tuberculous bronchial glands. Sometimes the respiratory sounds are audible some distance from the body, particularly at the end of inspiration. This may be accompanied by stridor and persists during sleep. Eustace Smith called attention to a systolic murmur heard over the sternum when the child's head is thrown backwards. X-rays are a great help in diagnosis, as they show a shadow in the position of the dullness. Bronchoscopy may demonstrate a

stenosis of the trachea or bronchus, but one hardly likes to recommend any procedure requiring an anæsthetic, as it may clinch the diagnosis all too completely. A blood count will show more or less anæmia with relative lymphocytosis. The tonsils will probably be enlarged and adenoid vegetations present. Other lymphatic glands may be palpable, and perhaps the spleen.

Prophylactic treatment consists in preventing the child from throwing the head far back, and from indulging in strenuous exercise. Emotional excitement is to be avoided as far as possible. Very hot or cold baths should not be allowed. Only absolutely necessary operations should be undertaken. Any catarrhal infections of the upper respiratory tract should be treated early and with great thoroughness. A Wassermann reaction should be done, if there is any suspicion of congenital syphilis, and appropriate treatment carried out if this is positive. If there are any signs of rickets, this also calls for treatment. Cautious treatment by X-rays is certainly helpful, and I have been favourably impressed with the effects of artificial sunlight, especially as this allows of complete utiliastion of any Vitamin A without giving too much fat in the diet. I have no experience of thymectomy, and should hesitate to recommend it, preferring to rely on irradiation. During an attack of thymic asthma, hot or cold compresses should be applied to the neck, and oxygen and cardiac stimulants given. Intubation with a long tube has also been recommended. Feeding with fresh thymus might be tried, but I am sceptical as to the value of thymic extract for the reasons already given.

The thymus may be the site of lymphomatous, lymphadenomatous, or lymphosarcomatous tumours. I have seen the blood picture of acute lymphatic leukæmia produced by lymphosarcoma of the thymus in a child of six. Epithelioma of the thymus, presumably originating in the epithelium of the third gill slit, has also been described.

### THE PINEAL BODY.

This is a small pinkish body situated under the posterior portion of the corpus callosum of the brain, and just over the anterior corpora quadrigemina. It is sometimes

called the epiphysis. In reptiles it has an anterior process which reaches the skin of the head, and which evidently represents the primitive median eye, since it contains fragments of a retina, while in some lizards, such as Hatteria, the skin scale over it has the appearance of an eye. In mammals it contains neuroglia as well as cells which have been regarded as secretory in character. It also contains " brain sand," such as is found in the choroid plexus and in the pia mater of the olfactory lobe. It may undergo cystic enlargement or degeneration, and may be the site of tumours.

The lowering of blood pressure which has been observed after injection of pineal extracts is probably of no importance, as this happens after the injection of so many tissue extracts. Destruction of the gland by the thermo-cautery in rabbits has led to death within 12 hours from hæmorrhage into the ventricles. But if the animals survived the first 24 hours no serious consequences were observed.

Glycosuria occasionally occurs with pineal cysts. This is probably due to the direct effect of pressure. More important is the condition known as " macrogenitosomia præcox," a rare condition, usually in children. There is premature physical and psychical development, the sexual organs being particularly affected, both as to enlargement and early function, growth of beard and body hair particularly in boys, change of voice, and adiposity. Eye defects are not uncommon, from pressure on the underlying anterior corpora quadrigemina and third nerve nuclei. Although psychical precocity is stated to be the rule, mental defects have also been recorded. Muscular dystrophies have been associated by some with disease of the pineal. I have seen a case of pseudo-hypertrophic muscular dystrophy accompanied by premature sexual development in a boy, and I was informed that his brother, who died of this disease between 12 and 13, had the appearance of a youth of 20. As already stated, the general view is that the pineal is a retarding structure, prolonging childhood and delaying sexual maturity in the interests of somatic growth. The above syndrome would, therefore, appear to be associated with defect, and not with overaction of

the pineal. No active principle has yet been extracted, and I have never satisfied myself of any therapeutic effect from administration of extracts of the gland. It seems probable that, in spite of the presence of cells which may be secretory, it really produces its effect through the central nervous system, as Llewellys Barker maintains. Its anatomical position makes this view plausible. The resemblances between overaction of the adrenal cortex and underaction of the pineal are suggestive, in view of the influence of the former in the development of the central nervous system.

## CHAPTER VIII

# THE ENDOCRINES AND THE GONADS

If, as biologists now believe, sex is determined by the pattern of the chromosomes assumed at fertilisation, it must have its influence on all the tissues of the developing fœtus. It is not likely that the endocrine system would escape from this influence, since it is so obviously associated with sex later on. I believe that pluriglandular syndromes often originate in gonadal disorders. But the converse also holds; changes in the endocrine glands can modify secondary sexual characters.

The close interaction of the endocrine system, particularly the thyroid, pituitary and adrenals, with the sympathetic nervous system on the one hand, and with the reproductive organs on the other, is a fact of paramount importance. Disturbance of one limb of this tripod must inevitably upset the balance of all three sooner or later. Mott held that the interstitial or Leydig cells of the testes, which consist of abundant polygonal cells with a round nucleus lying in a cytoplasm, staining well with eosin, had two chief phases of activity, one during fœtal life when they appeared to determine the physical and mental sexual characters, the other at puberty, when they influence the secondary sexual characters. Moreover, by the sensitising influence of the testicular hormone the primary male characters are, even before birth, made dominant in all the bisexual somatic cells. Lillie reports a case in which the female characters of a female twin calf were more or less completely suppressed and certain male structures developed as the result of anastomosis of the placental blood vessels with those of the associated male twin calf. This can only be explained by the influence of a soluble and diffusible hormone derived from the male and carried to the female by the circulating blood. It confirms Mott's view

that the testicular hormone is active at an earlier age than the ovarian, and he remarked that we can thus understand why castration, even in early life, cannot remove entirely the hormonic effect thus early impressed upon the nervous system and other tissues.

The source of the ovarian hormone is the Graafian follicle and it may be supposed that a continuous conversion of primordial follicles into immature Graafian follicles from earliest infancy onwards provides a feminising hormone to counteract the pre-established male dominance in the bisexual cells of the body. Should this follicle formation not occur to the normal extent, there must be a tendency to masculination. But here again öophorectomy cannot entirely undo the effects previously wrought on the body by the ovarian hormone.

The case for the formation of an internal secretion by the ovary may be regarded as proven, since Allen and Doisy (*Journ. Amer. Med. Assoc.*, 1923, Vol. LXXXI, p. 819) have prepared a hormone from it which has produced the œstral phenomena and growth of the mammary glands in öophorectomised animals. They state further that by means of injection of this extract young animals may be brought to sexual maturity from twenty to forty days before the usual time. These results have been confirmed by other workers.

That the testis forms an internal secretion is strongly suggested by the fact that the effects of ligature of the whole spermatic cord which would prevent any such secretion from reaching the circulation are much more profound on the secondary sexual characters than those of ligation of the vas deferens, which would merely stop the external secretion. The results of the former procedure more nearly resemble those of castration.

The first observations on the internal secretion of the testis were made by Brown-Sequard in 1889, who claimed that injections of testicular extract had an extraordinarily beneficial effect on himself at the age of 72. The element of auto-suggestion might well enter into these experiments ; the search for the elixir of life appears to have a strong fascination for scientists at about the age of 70. Since his day many experiments with such extracts have been made, but the results are far from

convincing. Their injection has not had much effect on castrated animals. Stanley used a semi-solid substance obtained from the testes of rams and goats on 656 men complaining of such varied conditions as asthenia, rheumatism, neurasthenia, and senility. About half of them reported definite improvement in their symptoms. But, as Kenneth Walker points out, this was an instance of the employment of heterografts rather than of extracts. The semi-solid masses he used could be felt for many weeks as nodules lying under the skin, slowly becoming absorbed and liberating during this process a certain amount of hormone. Where testicular extract has been given by the mouth there has been little if any clear proof of its efficacy. I have seen striking effects after its administration in cases of delayed puberty, but I have not been able to satisfy myself that these were due to the extract, and not simply because the condition improved naturally with the lapse of time.

Two operative methods have, therefore, been introduced. Steinach ligatured the vas deferens, believing that in this way the activity of the gland would be diverted from external to internal secretion. Voronoff used testicular grafts.

For conclusions as to the efficacy of these procedures I am indebted to the writings of Kenneth Walker. He says : " Those who are familiar with Steinach's experiments on aged rats must certainly be impressed by the results of vaso-ligature. Aged animals in a state of apathy and neglect showed after the operation of ligature increased activity, improvement in fur, alertness, increase in bodily weight, and a return of sexual vigour. It is true that after a period of regained health they relapsed again into senile apathy, but in spite of this the total length of life was greater than in the case of the untied rats. Macht, in America, has confirmed the statement that muscular co-ordination and vigour are increased in aged rats by vaso-ligature. In human beings the results of the operation have been less certain. In many cases no benefit has taken place. In some the general health and mental vigour of the patient have improved, and in a few cases the results have been still more striking. Much criticism has been levelled at Steinach's experiments. In

the first place it is by no means certain that the interstitial cells are responsible for the internal secretion of the testes, and personally I am one of those who regard them as trophic cells rather than the source of testicular hormone. However, even if this be the case and if Steinach's arguments, based on the increase of interstitial cells that takes place after ligature, be valueless, the bottom has not been knocked out of his experiments. Up to the present time I have performed Steinach's operation in some fifteen cases and, although it is difficult to eliminate the element of suggestion, I believe that in at least half of these cases an improvement in general health and an increase in mental vigour have taken place. I am particularly inclined to recommend the operation in the treatment of that hopeless malady of later life, paralysis agitans, having seen a very marked improvement in two out of four cases which I have treated in this way."

Next as to testicular grafts. "Here experimenters have been up against two obstacles, the first of these being that of obtaining material, and the second the difficulty in ensuring that the transplants become vascularised and survive the operation. In order to overcome the first difficulty, Voronoff and Thorek have made use of grafts obtained from the higher apes. The blood-relationships, as shown by Nuttall and others, and demonstrated by agglutination and precipitation tests, is very close between the higher anthropoids and man, and Voronoff considered that the chances of the survival of heterografts obtained from such a source would be far greater than if derived from the lower animals. He has now made some fifty or sixty transplants in the human subject, and claims to have obtained valuable results. The grafts have been undertaken for various conditions : eunuchoidism, senility, neurasthenia and sexual neurosis. In summing up his results, it would appear that the chief benefit has been in the direction of improvement in the general health, increase of mental and muscular vigour, and stimulation of the growth of hair. Less definite improvement has been noted in cases grafted for impotence or sexual neurosis. Other workers in this field have preferred to use human transplants and have derived their material, when opportunity occurred, from

newly executed criminals, patients dying of accident, and from cases of ' ectopia testis,' in which the removal of the misplaced organ was justified. It is from this last source that I myself have obtained my grafts. The technique of transplantations is not difficult. Personally, I think that Voronoff's use of a serous cavity like that of the tunica vaginalis for implantation is the best. The placing of grafts within the tunica vaginalis invariably provokes a reaction in which there is a pouring out of an exudate rich in nutritive substances. This exudate supplies nutriment to the engrafted tissue until vascularisation has taken place."

" Do these grafts actually survive, or is any benefit that accrues solely due to the absorption of liberated hormone ? Personally, I believe that the vascularisation and survival of the graft is an actual fact. At the same time I am convinced that a steady atrophy of the engrafted material occurs, and that the actual life of the transplant is considerably shorter than that claimed for it by Voronoff. Opportunities have occurred for the removal of a graft two or three months after operation and examining it histologically. Most observers, such as Ribbert and Herlitzka, have found that, although the grafts had become vascularised, they showed signs of regression, the tubules being replaced by cords, and the cells of the tubules reverting to a non-differentiated embryonic condition. Voronoff, however, has claimed that on one occasion on which a graft was taken from the testis of a young ram not yet arrived at the stage of spermatogenesis, the graft actually evolved in its host, and when removed subsequently showed the presence of spermatozoa. I find difficulty in accepting this statement. Other evidence of survival of the graft may be found in changes in metabolism, as shown by the respiratory exchange and by glucose tolerance curves. In a series of cases subjected to such tests I was able to show a distinct difference in the sugar curves before and after operation. How long a graft survives must still remain a matter of doubt, but I should have felt happy if I could be sure that complete atrophy had not occurred in eighteen months. But this does not necessarily mean that at the end of that period all benefit has been lost. In the first place certain

observations have been made which suggest the possibility that a graft may stimulate the growth of existing testicular tissue; secondly the hormone supplied by a graft may tide a patient over a critical period until compensatory changes in other endocrine glands have succeeded in restoring the endocrine balance. It must be remembered that the relationship between the testis and such glands as the pituitary and the suprarenals is a very close one. Fichera first showed that a hypertrophy of the pituitary body in castrated fowls occurred. An equally close relationship between the testis and the suprarenals is demonstrated by the occurrence of sexual precocity or of virilism in certain cases of suprarenal tumour. There is a direct connexion between the sex glands and the thyroid, and an indication that both the thymus and the pineal act as a brake on the activity of the gonads. This intimate association of the testes with the other members of the endocrine circle, although it has the advantage of permitting compensatory changes when the activity of the testis has been impaired, has corresponding disadvantages. In the majority of dystrophies that present themselves for treatment by means of testicular graft we are not dealing with a lesion confined to the testis, and too much must not be expected of the operation. Even when a case has begun as one of pure testicular deficiency, a graft will only confer a certain degree of benefit on account of the reciprocal involvement of other glands and of other structures that has taken place during the lapse of time. The longer the history of the deficiency the less hopeful is the outlook. An old castrate will not experience so much benefit from a graft as does a subject who has recently suffered testicular loss. It is frequently advisable to combine testicular grafts with the use of extracts of other endocrine glands, notably of the pituitary, the suprarenals or the thyroid."

This, I think, fairly summarises the present position of our knowledge. In one case of mine in which Mr. Kenneth Walker performed a grafting operation for a marked degree of eunuchoidism in a man of 34 following mumps with double orchitis at the age of 13, there was a decided improvement in all symptoms. Unfortunately about $2\frac{1}{2}$ years after the operation he developed signs of

intracranial tumour, for which decompression had to be performed; but there is no doubt that up to that time the improvement had been maintained. It is possible, in Dr. Gordon Holmes' opinion, that this "tumour" is really a cyst in the stalk of the pituitary. The results of implantation in animals of the primary sex glands into the opposite sex clearly show that the secondary sexual characteristics can be profoundly modified in that way.

All the ductless glands, and especially those co-operating with the sympathetic nervous system, participate in the development of sexual characters, the thyroid and possibly the posterior lobe of the pituitary tipping the balance towards feminism, the adrenal cortex and the anterior pituitary towards virilism. As far as the thyroid is concerned, the matter is comparatively simple; it is a survival from the uterus of the primitive arthropod ancestor, and throughout the child-bearing period shows increased activity at such epochs as puberty, the catamenia, marriage and pregnancy, undergoing partial involution at the climacteric.

The association of the pituitary with the gonads is more complicated. Neither the gonads nor the pituitary can develop fully without the other. I have repeatedly seen the association between gonadal hypoplasia and hypopituitarism. Overaction of the anterior lobe tends to virilism; the acromegalic woman always loses some degree of feminity, while the influence of the ovarian hormone on the secretion of the posterior lobe in the interests of maternity has now been clearly demonstrated. In 1923 W. E. Dixon showed that the injection of ovarian extract produced a definite secretion of pituitrin into the cerebrospinal fluid. As he found, on continuing this work, certain irregularities in the response, he extended his observations in conjunction with Marshall, with interesting and important results.

They found that the corpus luteum inhibited this effect and, as might be expected, the corpus luteum of pregnancy did so much more powerfully than that of œstrus or menstruation. I might point out that this apparently does not inhibit the stimulating effect of pregnancy on the anterior lobe of the pituitary, as the slightly acromegalic facies of pregnancy witnesses. Is

it possible that, by checking some of the activities of the posterior lobe, the anterior lobe has more effect? In any case, just before parturition, this inhibitory effect of the corpus luteum passes off; the stimulus of the rest of the ovary produces its full effect, pituitrin passes abundantly into the cerebrospinal fluid, thence into the blood stream, and excites the uterus to contract, an effect which it does not have on the virgin uterus. This explains Fränkel's earlier observation that the destruction of the corpus luteum of pregnancy by the cautery inevitably leads to abortion. As soon as the uterine contractions have led to the birth of the child, the pituitrin excites the secretion of milk. It is usually stated that this is merely due to its contractile effect on the muscles in the mammary ducts, but this would hardly explain a case at St. Bartholomew's Hospital, where a pituitary tumour was associated with continuous lactation for seven years. Mr. H. L. Wilson made a careful search in the ovaries at the post-mortem, and failed to find any evidence of the presence of a corpus luteum.

The headache sometimes experienced by women during the act of suckling appears to be due to the demand made on the pituitary. I have known this to be relieved on giving pituitary extract. I saw a woman who had developed bitemporal hemianopsia in the course of the first and only pregnancy, which occurred after more than twelve years of married life, during which she had only had twelve periods. Wilfrid Shaw finds that some contraction of the temporal visual fields occurs in 86% of pregnancies; but this was a gross change, and obvious without the perimeter. Her pituitary fossa was enlarged. She was unable to suckle her child on account of sore nipples, but she continued to lactate for two years in spite of treatment. I suggested administration of corpus luteum extract, and the secretion of milk stopped in ten days. Since then I have achieved the same result in a case of lactation lasting three years.

In the same way pituitrin seems necessary to the involution of the uterus after parturition. Leslie Pugh has found that failure of the corpus luteum of the cow to atrophy led to subinvolution and disturbance of the

œstral cycle, while destruction of it by massage per rectum removed these effects.

The most reasonable explanation of all this is that a close association exists between the gonads and the pituitary ; that the internal secretion of the ovary stimulates the secretion of pituitrin ; and that the development of a corpus luteum in pregnancy checks this process in the interests of the fœtus until the time for the uterus to contract and for the milk to flow, when this inhibition is suddenly withdrawn. If the corpus luteum persists the proper contraction of the uterus is prevented, while on the other hand an overstimulated pituitary may excite continuous activity of the mammary gland. The fact that the blood sugar curves of pituitary glycosuria and of the glycosuria of pregnancy are similar suggests that the latter condition is also due to pituitary disturbance, which is comprehensible, since pituitrin directly inhibits the action of insulin. This suggests that the normal hold-up of pituitrin during pregnancy allows sugar to be stored more readily in the interests of the offspring through the unchecked action of insulin, and that failure of this hold-up to occur leads to glycosuria. At certain times and seasons, then, the ovary develops the antidote to its own action in the corpus luteum.

The association between the gonads and the adrenal cortex is simpler and more direct. They arise from the same structure, the Wolffian body, and hyperplasia of the latter always stimulates the former. It is more difficult to explain why this stimulation always results in virilism. Krabbe maintains that an adrenal cortical tumour, which has this effect, develops from sex cells of the masculine type that in early embryonic life have become embedded in the adrenal cortex, and that the ovary, unlike the testis, is primitively bisexual. This would account for the virilism and harmonises to a certain extent with Mott's view. But it is by no means generally accepted.

Collett has recorded a remarkable case (*Amer. Journ. Dis. of Child.*, 1924, Vol. 27, p. 204) of a girl who showed signs of puberty at about six months old. The clitoris came to resemble a small penis. She grew much too fast. Under treatment by thymus gland for seven months she

appeared to improve. At the age of two a hypernephroma was removed, and the premature growth of hair nearly all disappeared, while the clitoris reverted to a more feminine type. This is the first recorded case of a child surviving the operation.

The following interesting case of hyperadrenalism with virilism came under my observation in 1924. A lady of 40 was brought to see me, with the following history. She had seemed nervous and ailing for more than a year when she developed a vesicular rash. About Christmas she had had a severe shock, after which her thyroid gland was noted to be larger, and she had tachycardia and tremors with some pyrexia, but so far from losing weight she put it on. X-rays were applied to the gland, after which she was said to show signs of thyroid deficiency; there were certainly supraclavicular pads of fat. Her mental condition altered considerably; she thought she was changing into something monstrous and strange, and became sensitive about seeing anyone. When I saw her in June, 1924, she produced a photograph taken about two years before, and there was no doubt she had altered in appearance. From a refined face with chiselled features hers had become full, florid and rather coarse, though certainly not masculine in type. It was not until later that I discovered that she carefully practised depilation, or otherwise she would have grown a beard and whiskers. Her blood pressure was curiously variable, but usually rather raised. Her general appearance was that of hypopituitarism, but the thyroid gland was still distinctly enlarged.

Her relations wished her to be under close observation in a nursing home, and here she confided to me the nature of her obsession. She felt that she was changing into a man! I regarded this as merely part of her mental alteration; her pelvic organs and her periods were quite normal; but in the course of routine investigation I had an X-ray examination made which showed a shadow over the left kidney. This was repeated a week later, and the shadow was larger and by this time I could feel something there, so I concluded I had a cortical tumour of the adrenals to deal with. Mr. Wilfred Trotter saw her with me, and agreed as to the plausibility of the diagnosis, and

with the propriety of my suggestion that a pyelogram should be taken. Mr. Girling Ball did this, and it showed that the left kidney was pushed down by something above and in front of it. Operation was decided upon, and with some difficulty he removed a large tumour of the adrenal. For 24 hours after the operation her condition seemed quite satisfactory; then her temperature shot up to 103, she became very flushed, her pulse rate rose to about 140, she was wildly excited, and she died about 40 hours after the operation, with all the signs of acute hyperthyroidism. The tumour proved to be an endothelioma of the adrenal, with cortical tissue spread out all over it.

It is interesting that the first symptom was the psychological change of which the patient was conscious, and that the thyroid enlarged as if to attempt to redress the balance in favour of feminism, becoming apparently exhausted in the process. Her death did not appear to be due to hæmorrhage or sepsis, and the feature of acute hyperthyroidism suggests that the removal of the greatly enlarged adrenal allowed the still enlarged thyroid to upset the balance completely.

Gordon Holmes, in reporting a similar case, in which operation was successful, has recently (*Quart. Journ. Med.*, 1925, Vol. XLIII, p. 143) reviewed the literature of the subject of virilism associated with adrenal tumours. Few would dissent from his statement that there is now conclusive evidence "that an internal secretion derived from the cortex of the suprarenal bodies when in excess tends in women to diminish the female and increase the male primary and secondary sexual characters." The special interest of this case is that the first symptom was an obsession which had been thought by several observers to have no objective basis, but which proved the clue to the recognition of grave organic disease.

He goes on to say, "Further, we may conclude that in addition to . . . the ovaries and testes, the hypophysis and perhaps epiphysis too, the cortex of the suprarenal bodies furnishes a hormone which plays an important part in the development and maintenance at a normal level of the genital organs and of the secondary sexual characters." It may be of interest to refer briefly to two

other cases of virilism in women, which help to throw some light on the condition in general.

A girl of 18 was sent to see me, with the history that up to 14 she had been normal, and that then she began to put on weight, to grow hair on her face, and to suffer from headache; she had never menstruated. As her condition evidently called for investigation, she was admitted to St. Bartholomew's Hospital.

She had a large rounded florid face. The hair on the scalp started further back than is usual in girls. She had a well-developed moustache, whiskers and some beard. Her fields of vision and her optic discs were normal. The palatal arch was not unduly high, and her lateral incisors were natural. The apex beat of her heart was a full inch external to its proper position, and the pulse was frequent (100–110), but regular. Her blood pressure was raised to 175 mm. systolic and 145 diastolic. There were a number of small petechiæ scattered over the face and back and some very large red striæ on the abdomen. Although her body was generally fat, the breasts were not well developed; the obesity did not extend to her arms and legs; the legs were distinctly cyanosed. The nail beds showed some staphylococcic infection. Axillary and pubic hair were normal. The uterus was small and undeveloped. The urine contained a cloud of albumen and rather more than 2% of sugar, but no acetone. Tube casts were found, though not at the first examination. A catheter specimen grew some streptococci and staphylococci. Her blood sugar was raised to 0·27%. The blood count showed 5,300,000 red corpuscles, 92% of hæmoglobin and 5,400 leucocytes. The basal metabolic rate was + 15%. The pituitary fossa measured 17 by 7 mm., and was therefore rather large. The clinoid processes gave a hazy shadow.

Dr. W. E. Dixon kindly examined the urine for pressor amines, but reported that these were not present to a greater extent than normal. On diet and 10 units of insulin daily her blood sugar fell to 0·1%, and the urine became free from sugar. Unfortunately a month after admission she developed an irritative cough, and the temperature rose. An X-ray of the chest showed an active inflammatory process in both lungs, which appeared to

be tuberculous. At her parents' request she returned home a week after this, and died two days later.

As no necropsy could be obtained, it might be thought that it was not worth while to report this case, but in the next somewhat similar case there was a necropsy, which enables some general inferences to be drawn.

A married woman, aged 26, was sent to see me in 1922 at St. Bartholomew's Hospital by Dr. T. H. G. Shore with a three years' history of hirsuties, amenorrhœa and obesity. She also suffered from giddiness, occipital headache, nausea and vomiting. A skiagram of the pituitary fossa was normal. Her blood count showed seven million red corpuscles, 120% of hæmoglobin and 14,800 leucocytes. There were some coarse cutaneous striæ. The urine was normal at that time. In 1925 she came under the care of Dr. Parkes Weber at the German Hospital, and he was good enough to give me the opportunity of observing her for a few days at St. Bartholomew's Hospital. She was very florid, with some hair on the upper lip, chin and cheeks. She had extensive retinal changes in both eyes and optic neuritis. The fields of vision were apparently normal. The palatal arch was high. Pyorrhœa was present. The heart was not obviously enlarged; the radial artery was not thickened; the pulse was rather frequent. The blood pressure was raised to 200 mm. systolic and 150 mm. diastolic. The spleen was not palpable. Obesity was chiefly confined to the pendulous breasts and abdomen. The skin showed large cutaneous striæ, some red, some pale, many purpuric spots and some telangiectases. The skin of the legs was shiny and pigmented. The external genitals were not abnormal, but the uterus was infantile; the right tube was undeveloped, the left was not felt. The blood count no longer showed polycythæmia or leucocytosis. X-ray of the pituitary fossa now showed hazy clinoid processes. The urine contained 0·1% of albumen, some red and white corpuscles, and some granular and hyaline casts. Dr. Parkes Weber had found a little glycosuria after 10 grammes of dextrose. The blood urea was 42 mgm., and the basal metabolic rate was + 20%. The Wassermann reaction was negative.

She died soon after this in the German Hospital from

acute pulmonary œdema. Dr. Parkes Weber has recorded the case fully in the *British Journal of Dermatology and Syphilis*, 1926, Vol. XXXVIII, pp. 1–19, and it is sufficient to say here that the necropsy revealed, in addition to chronic interstitial nephritis and cardiac hypertrophy, an apparent excess of adrenal medulla and no hypernephroma, but a basophilic adenoma in the anterior lobe of the pituitary.

These cases appear to belong to the group described by Achard and Thiers (*Bull. d. Acad. Méd.*, 1921, Vol. 86, p. 51) as the "diabetes of bearded women." They describe six characteristics, of which only the first three are essential: (1) Hirsuties on the face—masculine in type. Partial baldness of the frontal region. (2) Obesity. (3) Disturbed genital functions. (4) High blood pressure. (5) Cutaneous striæ. (6) Glycosuria, or lowered carbohydrate tolerance. Both cases here described showed all these features.

In the cases collected and described by Achard and Thiers the necropsies when obtained generally showed adrenal or pituitary tumours. Two other cases are referred to in Dr. Parkes Weber's paper already quoted. The case without necropsy showed an enlarged pituitary fossa, so that there was a strong probability of its being of the same type as the second. The haziness of the clinoid processes was also noted in Turney's case (quoted by Parkes Weber) of the adrenal type, and is apparently merely due to deficiency of calcium salts. It seems that a probable explanation of the symptoms in these two cases is that the pituitary lesion irritated the hypothalamus, which is regarded by some observers as the head ganglion of the sympathetic, while disturbing the pituitary functions. The sympathetic irritation would lead to the excess of the adrenal medulla, exciting glycosuria and high blood pressure, the latter leading to chronic interstitial nephritis. Both these cases showed an increased basal metabolic rate, which would also result from overstimulation of the sympathetic. I have not seen the basal metabolic rate referred to in other cases of this type. Certainly the combination of obesity with increased basal metabolic rate is a curious and striking feature. On the endocrine side the noteworthy feature

is the similarity of the signs produced by lesions of the anterior lobe of the pituitary and of the adrenal cortex.

I may recall the fact that both these glandular structures are in close association with nervous structures, the adrenal medulla being developed from sympathetic ganglion cells, and the pituitary being connected with the hypothalamus. Although pineal tumours cause sexual precocity with obesity, they do not tend to virilism, as do these lesions of the adrenal and anterior pituitary.

Naturally cases of virilism are not so likely to become pregnant, but Slocum has reported one where this occurred, and the beard and whiskers disappeared six months after the child was born when the catamenia returned. Virilism of this adrenal or pituitary type appears to vary in its manifestations according to the age at which the exciting condition occurs. (Apert.)

(1) During embryonic life it results in pseudo-hermaphroditism, the internal organs being feminine in type, while the external organs are malformed, approaching the male type.

(2) During infancy it produces hirsuties and precocious puberty ; in the female there is hypertrophy of the clitoris while the ovaries are small and cystic ; in the male there is testicular hypertrophy.

(3) After puberty the signs are as described in these cases—hirsuties, obesity and amenorrhœa being the most constant features.

(4) After the menopause there may be only hypertrichosis and obesity, though menorrhagia has been recorded.

As might be expected, the earlier the virilism is produced the greater the structural change ; while if it is induced during the child-bearing period the changes are mainly those of function.

It would be rash, in the light of such evidence as is here given, to conclude that minor degrees of virilism in women have no endocrine basis. It does not require a great disturbance of the endocrine balance to manifest such minor degrees, and they are not uncommon. War work and post-war customs have merely made it less usual for such manifestations to be repressed.

## CHAPTER IX

## THE ENDOCRINES AND GENERAL METABOLISM

It will be convenient to summarise some of the effects of the endocrine system on general metabolism, even though this may involve a certain amount of repetition. It is clearly recognised that the endocrine glands associated with the sympathetic nervous system are concerned with the activation of the body for defence. The method of response is essentially the same whether the body is activated against the external foe or against the internal foe of bacterial invasion. An important part of the reaction is the production of fever. Fever is known to be followed by changes in the adrenals or thyroid, and Cramer has shown that anything which calls for increased production of heat increases the secretory activity of these glands. Mere exposure of a mammal, but not of a cold-blooded animal, to a low temperature will have the same effect. The injection of tetrahydronaphthylamine will produce similar changes, together with all the phenomena of heat-stroke, and only exposure of the injected animal to cold will prevent a fatal issue. Any disease causing hyperpyrexia will induce these changes in the glands. Cramer showed that this increased secretion of the adrenals and thyroid flooded the blood with sugar, the increased oxidation of which materially increased the production of heat, and that, as long as the oxidative mechanisms were intact, glycosuria was not excited. Moreover, there would only be transient hyperglycæmia. But if they are impaired, hyperglycæmia will be more persistent. Thus we can understand the evil effect of focal sepsis in diabetes, for it further increases the already excessive blood sugar. The hyperglycæmia occasionally met with in infections indicates that there is

already a diminution in the efficiency of carbohydrate metabolism.

The other reactions to infection, tachycardia, shivering, sweating, calcium loss and increased metabolism, are exactly those which can be produced by an overacting sympathetic and thyroid. When the acute stage is over, as Vines points out, the anabolic functions of the parasympathetic should take control and promote healing. In this he believes the parathyroids share. Cramer believes, further, that this stimulation of the thyroid-adrenal apparatus explains the therapeutic action of non-specific vaccines, and even of proteins—the so-called treatment by protein shock. The effect of the injection of such substances is to produce a typical rigor. The rationale of this therapeutic measure would be that it elicits an increased functional activity from the thyroid-adrenal apparatus, in fact sympathetic fever, which is one of the normal reactions of the organism against bacterial infection.

Such an idea is consonant with the observed facts of the raised temperature so common in Graves' disease and in the subnormal temperature of myxœdema and Addison's disease.

Interesting support to Cramer's view can be derived from the fact that even in cold-blooded animals the thyroid acts as a rudimentary heat regulator. Thus in tadpoles kept at an unusually low temperature the thyroid enlarges, while if the temperature of the water is raised the gland becomes less active.

The mobilisation of sugar into the blood by the sympathetic-endocrine apparatus as a preparation for fight or flight is also comprehensible when we remember that active muscles require three and a half times as much sugar as resting muscle. That under civilised conditions such motor response often has to be repressed does not prevent the stimulation of this apparatus occurring. Pituitrin, adrenalin and thyroxin can alike antagonise insulin. As stated in the chapters on diseases of the respective glands, the form of the sugar curve appears to differ in each case, though Graham expresses it more cautiously by saying that these curves merely indicate impaired carbohydrate tolerance. It must certainly be admitted

that overaction and underaction respectively of the thyroid and pituitary do not regularly show the contrast one would expect.

The parathyroids act in the opposite sense to these glands; their removal increases the liability to glycosuria; their hormone appears to activate insulin (Cammidge), and therefore to co-operate with the pancreas. This is what might be expected on the view that the parasympathetic group produces the opposite effect on the blood sugar to the sympathetic group of endocrines. Conformably with this, B. C. Roy found that in sixteen cases of asthma, a condition typically associated with an overacting vagus, there was a low blood sugar in thirteen.

In the same way these glands have an antagonising effect on fat metabolism. Pituitrin transports fat from the outlying parts to the liver for metabolism there; hence patients with hypopituitarism are obese, and diabetics whose pituitrin is antagonised by insulin also tend to put on weight. Both adrenalin and pituitrin increase the fat in the liver and diminish the glycogen there; while insulin diminishes the fat and increases the glycogen. The antagonism between the adrenals and the pancreas is seen in other ways. Loewi's adrenalin mydriasis test is claimed as evidence of this; adrenalin normally dilates the pupil of the excised eye by stimulating sympathetic neuromuscular functions; in the intact eye this reaction does not occur in health. Something must inhibit the reaction. Loewi found that the reaction regularly occurred in depancreatised dogs, and therefore concluded that the pancreas was the source of this inhibition. The test has been used as a sign of pancreatic insufficiency; it gives a positive reaction, however, in hyperthyroidism also, presumably because the threshold to sympathetic stimulation is lowered thereby; I have also seen a positive result in acute appendicitis, again presumably because the sympathetic is already strongly stimulated, so that adrenalin can produce an exaggerated response. Further, excision of the adrenals has been followed by a dribbling secretion of pancreatic juice, which can be checked by adrenalin. So that the adrenals and the pancreas appear to have opposing

effects on the blood sugar, glycogen storage, fat metabolism, the long ciliary nerves of the pupil, and on the external secretion of pancreatic juice.

**Basal Metabolism.**

The introduction of the estimation of the basal metabolic rate into clinical work has given valuable results. By basal metabolism is meant the amount of oxidation taking place in the body at rest and after a twelve-hour fast. Clinically this is measured by the rate of production of carbon dioxide from the oxygen inhaled, and not by direct calorimetry. The figure, taken in relation to the surface area of the body, is constant for normal people of the same sex and age. An increased basal metabolic rate is one of the most characteristic manifestations of hyperthyroidism. In Gardiner Hill's hands it has enabled a distinction to be drawn between those cases of goitre which have increased and diminished thyroid activity. In Graves' disease the basal metabolic rate may be increased by 60% or even more. Repeated estimations give the most accurate guide to the progress of the case, and help to decide whether medical means have reached the limit of their capacity to help. If it remains over 30%, I generally consider that operative intervention is called for. In myxœdema, on the other hand, the rate may be diminished by 40% or more, and repeated estimations in a case under treatment by thyroid extract will show the measure of improvement, thus aiding the determination of accurate dosage. Disturbance of endocrine glands other than the thyroid does not produce comparable changes in this rate, for the thyroid is the principal accelerator of metabolism, but I have reported two cases of the pluriglandular syndrome known as the diabetes of bearded women in which it was increased by 15 % and 20% respectively. In pituitary overaction the rate is usually raised, and depressed in underaction, but this may be due to associated changes in thyroid activity, and in no case are the alterations of the same magnitude as in frank thyroid disease.

This naturally leads us to the brief consideration of obesity associated with endocrine disturbances. In

general terms, obesity is due to an excess of intake over output; in other words, too much food or too little exercise. But this is not the whole question; some small eaters are stout, and some lazy people remain thin. Temperament no doubt plays a part also; the ceaseless restless movements of some and the placid behaviour of others must have their influence. The endocrine make-up enters largely into temperament, and the basal metabolic rate, which depends so much on the endocrine state, must determine the tendency to obesity or the reverse. Defective action of the gonads, thyroid and pituitary, will each in their several ways tend to obesity; it is extraordinary that overaction of the adrenal cortex, which stimulates the gonads, should, nevertheless, have the same effect, and that in the diabetes of bearded women there should be obesity in spite of an increased basal metabolic rate. The part played by pituitrin in the transport of fat to the liver for metabolism there must be of great importance, for anything which interferes with this increases the amount of inert and therefore useless fat in the outlying parts of the body. During the food-rationing period of the War one saw that, though most people lost weight, some did not, and these appeared to lose strength more than the others. Several such that I examined presented stigmata of hypothyroidism or of hypopituitarism. In the same way, in later middle life, as the katabolic accelerator glands become less active, obesity becomes more common and less food is required. A child of five requires about 70 calories per kilo of body weight, whereas an active adult needs 30 calories, while when age advances 20 is sufficient. In extreme old age anabolism fails also, and thus, as Leonard Williams reminds us, the Justice with fair round belly gradually becomes the lean and slippered pantaloon. The distribution of the obesity which characterises the various endocrine disturbances has already been detailed.

**The Endocrines and the Influence of Climate.**

It is clear that the adrenals and the pituitary play a part in the production of pigment. It has been found that exposure of the skin of a brunette to a quartz lamp or to heat leads to an increase in its pigment. When

the adrenals have been injured this effect can be produced more easily. Similar changes have been brought about by dilute solutions of adrenalin. The presence of an oxidising enzyme in the skin is necessary to the production of melanin there. This enzyme is scanty in blondes, and absent in albinos. That the pituitary as well as the adrenals play an important part in the process of pigmentation is shown by the way in which tadpoles from which this gland has been removed become albinos. Moreover, pituitrin can control the changes in colour of the frog's skin. It causes the pigment granules to stream out into the branches of the pigment cells, so that they cover a much larger area, rendering the animal's skin much darker. Further, this appears to be due to a nervous reflex ; when the animal is on a light background stimulation of the retina is relayed as nervous impulses to the pituitary, causing it to diminish production, and the frog becomes lighter in colour. In this way we can understand how protective colouring can be regulated.

The subnormal temperature of persons suffering from disease of the anterior lobe of the pituitary, and the febrile reaction induced in them by the injection of its extract, shows again that there is a close association between the heat-producing glands and pigmentation. That blondes and albinos are ill-adapted to hot climates is well known. The French Government, I am informed, decline to accept anyone of fair complexion for service in the Congo or other tropical regions. Their experience is that fair men out there die off very quickly, and they will only appoint people like the Southern French, who have the power of developing protective pigment.

In 1909 Leonard Williams called attention to the influence of climate in moulding racial character through the endocrine glands ; but his conception was too much in advance of current medical thought then to receive the attention it merited. He pointed out that not only are there differences between the white man and the black, between Asiatics and Europeans, between the Latins and the Saxons admittedly and even obtrusively climatic in origin, but that modifications through climate can still be seen at work. He says—" In illustration of the last point I need only mention the fair skin and the

red hair which long residence in northern climes has conferred upon some Jewish families, and the stereotyping by the climate of the North American continent of the descendants of its widely dissemblant annual European recruits into the hatchet-shaped face and wiry frame of the Red Indian aborigines." He suggests that the skin may be compared to a sensitive plate, stimulation of any portion of which will produce reflex activities in some distant organ, and he regards the formation of cutaneous pigment as protective against such stimulation becoming excessive. The distant organs mainly affected in this way he believes to be the endocrine glands, and it is obvious from the examples just quoted that the adrenals and the pituitary play an important part in the pigmentary changes of the body. At the time the theory was put forward the close association between the sympathetic nervous system, the ductless glands and the higher levels of the nervous system was not sufficiently recognised to make it acceptable. But I think we are now justified in saying that climatic environment can modify our psychic "make-up" through the endocrine glands.

## CHAPTER X

# THE ENDOCRINES AND THE PSYCHO-NEUROSES

MANY years ago Hughlings Jackson spoke of the three levels of the nervous system, representing different evolutionary stages, and such an arrangement is now generally conceded. I shall adopt this classification in a modified form to explain my views of the relations between the endocrine system and the psychoneuroses.

We may look upon the evolution of the nervous system as passing through the following stages :—

(1) A stage in which the whole of the central nervous system corresponded to the present visceral or involuntary nervous system with its head ganglion in the hypothalamus—mainly confining its attention to the functions of the organic life, and entering into alliance with the still older chemiotactic mechanisms now housed in the endocrine glands. Its reactions were widespread, explosive and lacking in discrimination.

(2) A stage in which the central nervous system reached as far forward as the existing basal ganglia—practically representing the evolutionary stage of the fishes. Emotional expression and static control of the body were now possible. Corresponding with this, chemical mechanisms reached higher synthetic possibilities by the elaboration of the liver beyond the stage of a simple tubular gland. But the central nervous system influenced the metabolism of the liver through the highest ganglia then existing. It is only of recent years that we have appreciated that the mid-brain is associated with hepatic functions, although the pioneer work of Kinnier Wilson on the association between degeneration of the lenticular nucleus of the corpus striatum and cirrhosis of the liver gave us a clear-cut example some years ago. Lethargic encephalitis may show signs of hepatic insuffi-

ciency, while its Parkinsonian sequelæ have taught us a good deal about the mid-brain where its lesions mainly occur. Manganese poisoning provides another example of a toxic substance attacking the liver and the mid-brain alike. The evidence, therefore, of a functional association between the mid-brain and the liver is increasing. The evidence that lesions of the mid-brain can lead to deterioration of moral character and of behaviour has, unfortunately, been made only too clear by the sequelæ of lethargic encephalitis.

(3) The final stage where the development of the cerebral cortex made possible the performance of skilled voluntary movements and the inhibition of automatic movements and of excessive emotional expression. This level has been released from metabolic duties and thus set free for higher psychical development.

Psychoneuroses may, therefore, be associated with disturbances of any of these three great levels of the nervous system.

Since instinctive behaviour was originally directed by chemical tropisms, we can understand that the endocrine glands, which still manufacture chemical controls, will continue to influence such behaviour. Their association with the sympathetic nervous system will facilitate such influences. But just as the sympathetic is closely associated with the endocrine glands outside the central nervous system, so it is inextricably intertwined with the higher levels inside it. Hence, as Stragnell puts it, " No endocrine inferiority can be present without a psychological change, a retreat or a compensation." We may consider the psychological changes associated with disturbances of the individual endocrine glands.

### THE THYROID.

The necessity for thyroxin in the due maintenance of mental activity is well recognised. It has been one of the triumphs of thyroid medication that it has rescued many from mental hebetude or worse to a life of normal mental activity. The cretin is dwarfed in body and mind, but is curiously placid and adaptable, just as the sufferer from an excess of thyroid is irritable and intransigent.

The adult sufferer from thyroid defect, *i.e.*, myxœdema, is more likely to be conscious of failing powers, and is, therefore, apt to be morose and suspicious, referring internal difficulties to external causes, as we are all apt to do. More usually the mental attitude is one of resigned melancholy. Sometimes there are hallucinations of sight and hearing. But occasionally the patient with myxœdema may become acutely maniacal. I saw a patient with myxœdema repeatedly and he improved very much on thyroid treatment. Then I lost sight of him, and I thought that, as he had now found the appropriate dose of thyroid extract, he was treating himself. But later I found he had abandoned medical treatment to take up Christian Science. Perhaps this was the first sign of impaired mental balance, but, at any rate, he became violently maniacal and was removed to an asylum. Here it was recognised that he was myxœdematous, but in view of his mania they did not venture to give him thyroid. However, as he did not improve at all in three weeks, they put him on thyroid, with immediate benefit. He soon became sane and able to give his medical history, and the Superintendent communicated with me. He remained quite sane, dying some years later after an operation for gallstones. I have heard of other similar cases.

But children and adults whose hypothyroidism falls short of cretinism or myxœdema may also have their mental state greatly improved by thyroid treatment. In daily life one so often meets people whose condition does not amount to actual disease, but proclaims aloud their need for thyroid.

The thyroid has been called the gland of creation. Just as thyroid secretion is essential to reproductive activity, so it is needed for every kind of creative activity, mental or artistic. Some time ago Crichton Miller asked if anyone had ever heard of a myxœdematous artist. Tredgold replied by citing a cretin at Zurich in the eighteenth century, who was an artist of some repute. But possibly he was really only achondroplasic. Crichton Miller has returned to his point and asked for cases of subthyroidic creators—be it of works of art or of children. It is, of course, true that a subthyroidic

woman may have children after she had had thyroid treatment. He further maintains that child-bearing and artistic creation are mutually exclusive, the store-house of creative energy being unable to cope with both kinds of creation. And I think that, though we can find apparent exceptions to this rule, it is very rare for both kinds of creation to be possible simultaneously.

Crile says—" I have never known a case of Graves' disease to be caused by success or happiness alone, or by hard physical labour unattended by psychic strain, or to be the result of energy voluntarily discharged." Sufferers from this condition are always irritable and tend to be explosive. Thoroughly unreasonable, they regard themselves as the only righteous persons in a wicked and froward world. " Oh, cursed spite, that ever they were born to set it right," is the burden of their lament. We have been reminded that Shelley had a hyperthyroid face. He certainly represented the hyperthyroidic temperament at its best. Of his creative genius there is no doubt, but in practical matters he beat his wings ineffectually against the bars of his cage. Indeed, his friend Hogg compared him with an albatross, magnificent in flight, but merely grotesque in captivity.

This difficulty which the sufferer from hyperthyroidism always experiences with her environment, not only makes her " gey ill to live with," but may precipitate her into actual insanity with suicidal tendencies. The thyroid gland is apt to enlarge in nerve storms, while in the manic-depressive psychoses I have seen the excited phase accompanied by signs of an overactive thyroid, to be replaced by signs of underaction as the phase of depression comes on. The influence of fright and repressed sexual emotion in the production of hyperthyroidism has already been dwelt on.

### THE PITUITARY.

This seems to play a special part with regard to rhythmic functions, and on the psychical side to show this in the direction of music and dancing, or on the more intellectual side with mathematical or more imaginative interests, widely as the last two seem to differ. Probably

the state of the other endocrine glands and of the cerebral cortex determines in which of these directions energy will be directed. Minor degrees of increased action of the anterior lobe results in a tall hairy man, long in tooth and big in jaw, with large broad hands. He often has a good intellect, with an imaginative force which can be controlled and brought to the service of his active brain; he is often musical; in short, a practical visionary. Unfortunately the effect of an overactive anterior lobe is not always so balanced as to produce such a happy result. Thus in the following case the amount of pituitary disturbance was not great, though the effect on character was disastrous. A young man of 23 was brought to see me, who had been very late in learning to walk and talk. He showed me two photographs of himself taken at the age of 4 or 5—one of these looked like a normal child, while the other looked degenerate. By the age of $6\frac{1}{2}$ he had developed the habit of lying. He grew rapidly to the height of 6 ft. 5 in. His palatal arch was very high, and his knuckles were very large. He was a confirmed liar and thief, and was suspected of deliberate and wilful arson. Gigantism due to overaction of the anterior lobe before the epiphyses are united may be followed by degeneration of the gland. The fossa becoming too small for the gland, the patient is apt to develop moral and intellectual inferiority, to suffer from compulsions and obsessions and to lack inhibitions. As Berman puts it, such individuals are "pathological liars with little or no initiative or conscience . . . As children they lie and steal, have enuresis, have poor control over themselves, and a low learning capacity." This patient showed all these points. But it is a little difficult to explain why, even while the pituitary was actively stimulating growth, there was a failure of the moral sense and intellect to develop. In the present state of our knowledge we can only say that there may have been a diversion of the pituitary action in one direction at the expense of others. Dr. Crichton Miller has suggested to me that it is rather due to failure on the part of other endocrine glands. In connection with Berman's view that the posterior lobe is concerned with the affections it is interesting to note that this youth had never shown the slightest affection for

anyone. It had been suggested that he should be certified as of unsound mind. On that I wrote to his doctor as follows :—" We are up against the difficulty which always arises between the medical and legal view of responsibility. I think that, in spite of his plausible manner with strangers, he has a criminal type of countenance ; and I should never be surprised at his doing something to justify that harsh saying. But the law which gives the dog one free bite would certainly not allow him to be deprived of his liberty." The sufferer from pituitary disturbance seems to compensate for his feeling of inferiority by craving for the limelight. The craving of the fat boy in Pickwick was to make people's " flesh creep."

The higher-grade sufferers from hypopituitarism compensate in a better way by persistent conscientious effort, often in excess of their physical strength.

It has been said that the anterior lobe tends to produce virile characters, and the posterior lobe feminine characters. The flat-chested, long-toothed, large-jawed, clumsy-handed woman, fondly believed by the French caricaturists to be typically English, is certainly suggestive of an exaggerated anterior pituitary, and she is not remarkable for feminine characteristics. A little side-issue of some interest occurs to me here—we are all familiar with the inseparable couple of women friends. One of the two usually adopts a somewhat masculine rôle, and I have been struck on several occasions to note the number of signs she presents of overactive anterior pituitary.

### THE ADRENALS.

The medulla, being really a part of the sympathetic nervous system, is brought into action as a defensive mechanism in rage, pain, and fear. For fear is really a perversion of a defensive mechanism. " It is especially intense when there is interference with any form of reaction to danger " (Rivers). But just as we cannot conceive that all the primitive sensations of a lower animal have the affective intensity of pain as we experience it, so we must not regard the emotional response of an animal to danger as having the affect of what we mean

by fear. To do so would be to fall into the common error, as Parker says, of interpreting the activities of the simpler animals as though they were miniature human beings. The much scantier associative mechanisms in the nervous system of lower animals precludes such an idea. The late A. C. Benson said: "It is strange to note the perpetual instinctive consciousness of danger which besets birds in the open; they must live in a tension of nervous watchfulness which would depress a human being into melancholia. . . . Do we realise what it must be to live, as even sheltered birds do, in a quiet garden, with the fear of an attack and death hanging over them from morning to night?" The best answer to this anthropomorphic view is that the behaviour of birds gives no suggestion of their being depressed into melancholia. Doubtless, when the appropriate motor response is prevented, the lower animal feels both pain and fear, but that all its sensations and emotions are thus coloured is most improbable, when we consider the much simpler structure of its nervous system.

It might be argued, on the other hand, that, as sensations of fear at once arise when the inhibiting mechanism is in abeyance, as in night terrors, in the induction of anæsthesia or in exhaustion states, fear must be a primitive emotion of great strength and universally present in lower forms of life. But I would urge that it is only in the stage when the associative mechanisms have been evolved and before these have been controlled by the higher levels that this is the case. Or, as Carpenter says: "Fear only becomes a mental stimulus at the time of or after the evolution of self-consciousness." The behaviour of savages supports this view. Fear, whether of evil spirits, of magic, of the dark, panic fear dominated primitive man and, whenever our resistance is lowered by disease, by shock or by psychic conflict, we betray our ancestry. That strange, primitive being which lurks in the unconscious mind of us all, peeps out. Elaboration of ceremonial and ritual is the first step taken by primitive man to counteract this; all religions pass through the "God-fearing" stage. Then with the higher development of the mind, and the recognition of the reality principle, comes release from such obsessions of

fear. In the disintegrative process of disease this higher control fails and phobias develop, which cannot be effectually exorcised by the ritual of a compulsion neurosis.

The adrenal medulla from its activating effect on the sympathetic is a fighting gland. And as the adrenal cortex tends to virilism, the owner of a well-developed pair of adrenals is pugnacious and masculine in type, with plenty of drive, not to say aggression. If the adrenals are in defect we see a weakening of all these characteristics, with a tendency for the vagus to get the upper hand, which may precipitate such things as asthma. If the adrenals are in excess we find a liability to anxiety neuroses, and to phobias of all kinds. In such an individual the dominant emotion is fear.

I have already illustrated this by the case of a woman with a cortical adrenal tumour, who was possessed by a phobia of becoming a man, thus combining the motifs of virilism and fear.

We do not know much about the psychological aspects of the *parathyroids* beyond the fact that they exert a sedative effect on the central nervous system, and that chronic defect in their action in children is associated with mental deficiency. For the rest, their activity seems to be chiefly concerned with control at the motor level. Defect in the retarding action of the *pineal* is associated with premature sexual and psychical development, though here, too, mental defects are not uncommon. Persistence of the other retarding gland, the *thymus*, produces, in addition to status lymphaticus physically, a " mother's darling " psychologically.

But this brings me to the much more important question of the psychological aspects of *infantilism* in general.

Sir Arthur Keith has recently made the profound remark that the tendency to carry youthful characters into adult life has played a large part in the evolution of human races. He was speaking at the time of the variations which differentiated man from the anthropoids, and which first appeared in fœtal or young apes ; but, like many of his remarks, it has a much wider application. The power of carrying youthful characters into adult life

turned an ape into a man, but just as it may be a source of strength, so it may become a besetting weakness. Its function is to maintain a plasticity out of which higher characteristics can be moulded ; its weakness is that the childish or primitive attitude may persist. As ever, evolution offers a higher or lower path. To a certain extent we all tend to grow up in patches. Not many of us can truthfully say, " When I became a man I put away childish things." I venture to suggest that the infantile psychical attitude in the psychoneurotic is merely the weak side, the unadapted side, of a principle which has a higher evolutionary value. This would account for the wide prevalence of this feature. Even the tadpole experiences a stress during metamorphosis into a frog ; it loses weight, and there is an appreciable mortality rate. It is hardly likely that the human being should escape " growing pains."

Of the ordinary endocrine types of infantilism I have already spoken. When one turns to more general difficulties in growing up, one finds, as might be expected, that the origin often appears to be gonadal, since reproduction is the characteristic which most definitely distinguishes the adult from the child.

In my opinion the process of self-starvation, *anorexia nervosa*, not uncommon in growing girls, and rarely seen in boys, is due to this difficulty in growing up. It has been graphically described by the late Sir Clifford Allbutt as follows : " A young woman thus afflicted, her clothes scarcely hanging together on her anatomy, her pulse slow and slack, her temperature two degrees below the normal mean, her bowels closed, her hair like that of a corpse, dry and lustreless, her face and limbs ashy and cold, her hollow eyes the only vivid thing about her—this wan creature, whose daily food might lie on a crown piece, will be busy with mothers' meetings, with little sister's frocks, with university extension and with what you please of unselfish effort, yet on what funds God only knows. At meal times her mother may cry, her father may storm, her friends may banter, and the cheerful reply never fails that she has eaten amply ; or, if not, that she can eat no more."

Anemorrhœa, or at least gross irregularity of the

periods, is a constant concomitant of this condition, and the sufferer is generally underdeveloped sexually. She usually dislikes the idea of growing up and of assuming more adult responsibilities. But, in addition, there is almost invariably a strong complex, usually involving undue dependence on the father and hostility towards the mother. I have only seen three cases of anorexia nervosa in young men; in two there were religious obsessions; in one of them there was a strong reaction against a dominant father; the other was a Parsee, and I know nothing about his parents, who were in India. In the third patient there was a fierce hostility towards the mother, but he was a homosexualist. In all the male cases the self-starvation was clearly connected with a perverted attempt at sublimation.

But, further, I believe that behind anorexia nervosa lurks the shadow of *dementia præcox*. Krapælin's description of the condition has led to a mental picture of this grave disorder, which is perhaps too definite; at any rate, there appear to be minor degrees, in which the prognosis is not quite so grave, and I regard anorexia nervosa as one of these. In typical dementia præcox the personality is introverted, while in anorexia nervosa it is often extroverted. If in the latter condition introversion occurs, in my opinion the outlook is more serious, because it is tending to dementia præcox.

Dementia præcox shows an atavistic reversion in bodily structure, as evidenced by the monkey-like hands, and a gonadal deficiency with a consequent persistence of an infantile outlook, together with morbid changes in the nuclei of the cortical cells of the brain. Hence there is a failure of adjustment to the conditions of adult life; the brain defensively withdraws itself from its environment, and consequently undergoes rapid involution. Mott made the important observation that there is a signal tendency of the offspring of insane parents to develop signs of insanity in adolescence, and that this accords with Darwin's law of Antedating or Anticipation. Those individuals who suffered from dementia in adolescence would have little chance of surviving the struggle for existence. Among civilised people insanity leads to segregation, and thus prevents propagation. The

regressive atrophy of the testes in males would also interfere with propagation. Again, females predisposed by hereditary tendency break down in adolescence under the stress of normal physiological conditions, such as pregnancy, parturition or lactation. Cases of so-called puerperal mania often terminate in dementia, and show a regressive atrophy of the ovaries. Only about 10% of the primary dementia female cases in asylums are married women, and very few of them have more than one or two children. In this way nature appears gradually to eliminate the mentally unfit by bringing the disease on at an earlier age, and in an incurable form. The gonadal defects, therefore, appear to be protective so far as the race is concerned. From a former chapter it will be seen how frequently a gonadal defect is associated with a pluriglandular syndrome.

In conclusion I may quote Pottenger, who says : " The great number of disease processes which express themselves in the vegetative structures (*i.e.*, autonomic nervous system and endocrine glands) . . . either interfere with the mechanism of defence or the providing of the organism with sustenance . . . and the individual who has an abnormal vegetative balance wages his struggle for existence with a handicap. . . . The ultimate effects are distributed to every system of the body, vegetative, voluntary and psychic. Between the vegetative and psychical systems a vicious circle is established, and each harmful stimulus in the one influences the other. Every disease process of a serious nature, therefore, must have a psychical side to it."

## CHAPTER XI

## ENDOCRINE THERAPY

As Starling pointed out more than twenty years ago, whenever we give a drug we imply thereby a belief that the functions of the body can be influenced by chemical means; and nothing would appear more reasonable than to use intelligently in disease those very drugs by which the body is enabled to do its own work in health. But it must be observed that before endocrine therapy can claim a rational basis it must be shown that—

1. The gland in question forms an internal secretion.
2. That active principle or principles of this secretion can be extracted.
3. A method of administration of this extract can be found which will admit of its utilisation by the body.

Now it must be admitted that the instances in which these criteria are all satisfied are few.

Endocrine therapy, indeed, has not kept pace with the increase of our knowledge of the endocrine system. In one sense this has been as well; for the way in which extracts were often ignorantly given would inevitably have done harm had they been potent. The damage that an injection of secretin can do to a fasting animal illustrates this.

Endocrine therapy may have as its object the replacement of a deficient internal secretion. With thyroid extract and insulin we are here on sure ground; with parathyroid, ovarian, and pituitary extract on less certain ground; with the remainder on very doubtful ground. But it may also have as its object the employment of some extract simply for its pharmacological action, such as adrenalin for its local vaso-constrictor

effect, or for other effects involving its stimulating action on the sympathetic, as in asthma. Pituitrin may similarly be used for its stimulating effect on plain muscle as in paralytic distention of the bowel.

Thirdly, I should include under endocrine therapy methods which have as their object the use of other drugs, which, by their influence on the endocrine glands, enable those glands to carry out their normal function more satisfactorily. This measure may have a future of considerable promise, for substitution therapy can never exactly imitate the steady drip of a hormone into the circulation, but at present the only definite example is the use of iodine medication in diseases of the thyroid; though it seems probable that vitamins may be exploited to that end.

Next we may consider methods of administration :—

**(1) Oral Administration.** Organo-therapy won its first great triumph with thyroid extract, and there was considerable disappointment because other glandular extracts failed to give commensurate results. It was not realised that, as thyroid secretion originally entered the alimentary tract by the thyroglossal duct, this might account for the ease with which it is absorbed from that tract. This probably applies to the parathyroids also. Then the anterior lobe of the pituitary is an outgrowth of the alimentary tract, though before the respiratory tract had been separated from it. This might lead us to expect that oral administration of pituitary extracts, at any rate if prepared from the anterior lobe, might be effective, though here the results are much less constant. Hamill has, however, observed uterine contractions produced in the cat by administration of pituitrin through the stomach tube after ligature of the pylorus. He has also seen post-partum oozing of blood from the uterus checked by oral administration of pituitrin, to return when the drug was discontinued and to cease when it was resumed. In a case of chronic intestinal atony I first injected pituitrin with good result, and later on gave it by the mouth, with the same result. Gardiner Hill has lowered blood sugar by oral administration of anterior lobe extract. I omit cases where the element of suggestion could have come in, but it would appear

that oral administration is occasionally effective, though it is difficult to explain the inconstancy of the result. The effect of the oral administration of other extracts is, to say the least of it, very uncertain, apart from the local effect of adrenalin on the gastric mucosa, as in the control of hæmatemesis and of vomiting. Blum, however, has reported reduction of the blood sugar from lingual administration of the hydrochlorate of insulin, though two to three times as large a dose was required. For the rest, we do not know whether the active principle can escape the action of the digestive ferments.

(2) **Nasal Administration.** It was suggested by Blumgart that, as the pituitary is more strictly an outgrowth of the nasal mucosa, its extracts might be more easily absorbed by spraying into the nose or from plugs of cotton-wool soaked in a solution of the extract inserted high up into the nasal cavity. This method has met with a fair degree of success in the treatment of diabetes insipidus by pituitrin. It is also believed by some observers that adrenalin may be absorbed by this route, as they have seen effects on the blood pressure after free application of this drug to the nasal mucosa as a preliminary to operations there for its local vaso-constrictor action.

(3) **Rectal Administration.** Very little is known of this method, but Stewart and Rogoff report reduction of blood-sugar by large doses of insulin given with blood, serum or water *per rectum*.

(4) **Subcutaneous or Intravenous Injection.** It is clear that adrenalin, pituitrin and insulin can readily produce powerful effects when given in this way. Parathyroid and ovarian hormones have recently been prepared which also seem highly effective when injected.

(5) **Grafting and Transplantation Methods.** This is still on its trial. It would appear that such grafts are treated by the organism as foreign bodies and become absorbed, so that their effect is only temporary. It may be that a graft is more likely to take root if it is inserted into an homologous tissue, such as the testicular grafts of which so much is heard to-day. Hurst was able to get an adrenal graft to take and to remain effective in the testis for over two years ; and it seems to me that

this might be associated with the fact that the interstitial cells of the testes and the cortex of the adrenal have a similar origin.

It would add very much to the accuracy of our observations on endocrine therapy if biochemical tests could be devised to demonstrate the effects of an extract. At present we have two such—the effect on the basal metabolic rate and on the blood sugar. These have already yielded valuable results, particularly in diseases of the thyroid and in diabetes respectively, but are probably capable of wider application. Kenneth Walker, for instance, has used them in studying the effects of grafting operations. I look forward to the introduction of biochemical tests on the lines of those employed for investigating hepatic efficiency. Loewi's adrenalin eye-test, Götsch's intradermal test, the diastase test, and tolerance to quinine hydrobromide, as employed by Bram, are probably capable of modification so as to yield objective evidence of the efficacy of an endocrine preparation. Vines has assayed the activity of parathyroid extracts by their power of destroying guanidine, and their therapeutic effect by estimating the calcium content of the blood.

Of late there has been some conflict between the physiologist and the clinician on endocrine therapy, which is due on the one hand to the laboratory worker not realising the urgency of the problem a sick man presents, and to uncritical enthusiasm, and, I may add, undue suggestibility on the part of the observer at the bed-side on the other hand. The physiologist can select his problem and can make use of rigid controls. The clinician has his problem thrust upon him, and has to attempt a solution without the aid of proper controls. Moreover, in the artificial world of the laboratory the selected problem is deliberately reduced to its simplest terms, as, for instance, by excluding a large part of the body from the circulation. Thus, a conception of blood-pressure emanated from the laboratory which did not take into account the extraordinarily complicated adjustments which occur in disease. The physiologist is rather too apt to apply the results of laboratory experiments to man, although the striking difference between

the effect of morphine on the cat and on man is ever before him, and although clinical evidence clearly shows digitalis does not raise human blood-pressure. He told us that pituitrin was a diuretic, although under clinical conditions its antidiuretic effect can be constantly demonstrated. But if the laboratory worker is not guiltless, we must admit that we are the greater sinners when we use glandular preparations which cannot be shown to contain the active principle, or which may even come from a gland which contains no active principle at all, and then attribute the patient's improvement to the medicine. I am not condemning the use of extracts that have not, as yet, received laboratory sanction, for some of our methods must remain empirical, and, as Timme reminds us, "the abysmally ignorant South American savages who gave us quinine did not even know its formula." But I am pleading for a more critical attitude towards our results. Indiscriminate pluriglandular therapy has led some laboratory workers to challenge the very existence of interactions and antagonisms of the different endocrine glands in association with the vegetative nervous system, yet others of them have recently obtained results which support this conception.

We may fairly claim, on the evidence given in the foregoing chapters, that the theory of co-operation between the adrenals, thyroid and pituitary on the one hand, and between the pancreas and parathyroids on the other, and of antagonism between these two groups, has a considerable body of experimental support, as there is also for the view that the gonads and the sympathetic nervous system interact with the former group. But if pluriglandular therapy has a rational basis, one must admit that it is generally irrationally applied without reference to potency, dosage, or method of administration. It has been pointed out that most pluriglandular preparations contain thyroid extract, and that the actually observed results may generally be attributed to its presence alone.

Agnosticism has been carried to the point of doubting that the observed pharmacological actions of adrenalin and pituitrin have any relation to the functions of the structures from which these extracts are prepared. But

I can hardly believe that the body is so ill-designed as that. To attribute such facts as those already given to the long arm of coincidence is surely to display credulity similar to that with which we are taxed. It is scientific Nihilism, in face of which I prefer to believe in the definite plan of the endocrine and vegetative nervous systems already described. Otherwise the body of experimental and clinical observations that has been collected is meaningless. Accepting it, we have a rational basis for endocrine therapy.

To summarise the therapeutic uses of each hormone in turn.

**The Thyroid.**

Thyroid medication has the widest application of all the endocrines, and is the easiest in practice. Apart from its use in frank cretinism and myxœdema, which need not be further considered, it should be employed in all cases of minor degrees of thyroid defect, and for "rheumatic" symptoms, asthma and enuresis when these are accompanied by any stigmata of hypothyroidism. Its importance must be remembered in pregnancy when there is any suggestion of thyroid weakness or where previous children have shown such weakness. In cases of defective growth it may be of great service, combined with pituitary (*see* Chapter V). It may be used in the treatment of obesity if this be due to endocrine defect, but not when the increase in weight is merely due to over-feeding, for then its accelerator action on the heart without augmentation of the beat may prove harmful. Considering the liability of the myxœdematous subject to atheroma it seems reasonable to employ thyroid extract in arterio-sclerosis, and since thyroxin dilates the smaller blood vessels and improves the peripheral circulation, this method may help to lower blood pressure. It certainly seems helpful in suspected cerebral thrombosis, and is worth trying in Raynaud's disease and chilblains. From the impaired nutrition of the skin in myxœdema Byron Bramwell argued that thyroid extract should be useful in skin diseases presumed to be associated with deficient metabolism, such as psoriasis, chronic eczema, ichthyosis, prurigo and

dermatitis herpetiformis. I have also found it useful in the pruritus of jaundice.

When an enlargement of the thyroid gland appears to be due to an attempt at compensation, thyroid extract is, of course, indicated: in cases of thyroid instability it should also be given, though in small doses. It is naturally contra-indicated in hyperthyroidism, toxic adenomata of the thyroid, or indeed in any condition accompanied by an increased basal metabolic rate.

I must repeat the caution against over-dosage. A total daily dose of 6 gr. of the extract of fresh gland seldom needs to be exceeded, and it is wise not to start with more than ½ gr. three times a day. Thyroideum siccum is five times as strong as the extract of fresh gland. Elixirs of thyroid are simpler for children, but their strength in terms of dried extracts should be known. An acceleration of the pulse is the readiest indication of over-dosage.

**The Parathyroids.**

Oral administration of parathyroid extract certainly seems to be effective, since it can raise the calcium content of the blood. Now that the hormone is available for injection, we shall no doubt be able to achieve more definite therapeutic effects with the drug. But even now cases of tetany and sprue seem to be improved by it, and it is worth trying in cases of ulcers, whether of the skin or of the stomach and duodenum. I have found it helpful in the functional albuminuria of rapidly growing boys. It is curious that it should have been recommended for chilblains as well as its antagonist, thyroid extract, but presumably thyroid diminishes the stasis, while parathyroid diminishes the serous exudate. For this latter action it has been recommended for urticaria. I have not been much impressed with its value in epilepsy, chorea or paralysis agitans. I do not think a dose of 1/10 gr. in the day need be exceeded as a rule, and overdosage may cause a feeling of profound malaise.

**The Pituitary.**

Extract of the whole pituitary gland should be given in cases of defective growth and development based on a pituitary defect. I generally give 2 gr. twice a day,

combined with some thyroid extract. Injections of ½ to 1 cc. of pituitrin are very useful in paralytic distention of the bowel, for diabetes insipidus, and as an oxytocic. This has been advised also in hypoglycæmic collapse after an overdose of insulin, since pituitrin and insulin are directly antagonistic, but there are better and safer methods. It is useful in asthma and, though not as striking in its action as adrenalin, may sometimes be combined with this drug to prolong its effect. It is a temporary cardiac stimulant, and may be tried in shock. Subinvolution of the uterus, uterine hæmorrhage and dysmenorrhœa, may yield to its administration. It has been recommended for pituitary headaches, but in that case it can only act by relieving the gland from some of its secretory duties. This is supported by the fact that such headaches may be associated with lactation, which makes special demands on the pituitary gland.

**The Adrenals.**

I am sceptical as to the value of the administration of any cortical extracts. Adrenalin, the secretion of the medulla, is well known to have a vaso-constrictor action, for which it is employed in eye work and in operations on the nose and throat and bladder. It is useful in epistaxis, and I think it worth trying in hæmatemesis in doses of 10 to 30 minims of the 1 in 1,000 solution in half an ounce of water every 4 hours by the mouth. But it should not be used in hæmoptysis, since it has little if any constrictor action on the pulmonary vessels. In the form of an ointment it is sometimes useful for hæmorrhoids. For its vaso-constrictor action it is often used in conjunction with local anæsthetics, as it delays the spread of the drug and permits of a more intense, localised, and prolonged action of the anæsthetic. Basil Lang recommends the following solution of different strengths, but all, as far as possible, isotonic with blood.

| | A. 0·4 *per cent.* | B. 0·8 *per cent.* | C. 2 *per cent.* |
|---|---|---|---|
| 4 per cent. novocaine with 0·1 per cent. thymol with oil of gaultheria .. | 1 cc. | 2 cc. | 5 cc. |

| | A. 0·4 *per cent.* | B. 0·8 *per cent.* | C. 2 *per cent.* |
|---|---|---|---|
| 4 per cent. saline with thymol and oil of gaultheria .. .. .. | 2 cc. | 2 cc. | 2 cc. |
| 1 in 1,000 adrenalin with thymol and oil of gaultheria .. .. .. | 3 drops | 3 drops | 3 drops |
| Distilled water up to .. | 10 cc. | 10 cc. | 10 cc. |

The most dilute solution is for fine nerve terminals; the larger the nerve trunks to be anæsthetised, the stronger should be the solution employed.

Langley urged the use of 20 minims of the 1 in 1,000 solution in water before food in cases of cardiospasm, and it is worth trying. For its sedative effect through the inhibitory nerves on the stomach I have given 10 to 30 minims of this solution for vomiting and obstinate hiccough with success. Exner found that by delaying absorption it was helpful in preventing the action of poisons; it may certainly be given pending the employment of other measures.

Perhaps its most dramatic effect is in asthma. The earlier it is injected during the paroxysm, the more effective it seems to be; the dose of 3 minims or even less may then check the attack, whereas 10 minims would be less useful later on. Hurst, therefore, considers that asthma is one of the diseases for which the medical man is justified in teaching the patient the use of the hypodermic syringe; if he puts the appropriate dose in the syringe before going to sleep the patient can administer the dose himself as soon as he is awakened by the onset of an attack; he will then probably abort the attack and fall asleep again. I am sure a great deal of distress and exhaustion can be avoided in this way. The same method is very useful in angio-neurotic œdema, though here larger doses may be required.

The effect of adrenalin on blood pressure is so transient that it can be of little avail in the treatment of low pressure. But in an emergency, such as heart failure during anæsthesia, the injection of adrenalin into the

heart or pericardium has sometimes produced striking benefit.

Parkinson and others have strongly urged its use in heart-block, because it can facilitate conduction through the auriculo-ventricular bundle. They are of opinion that the subcutaneous injection of 5 to 10 minims of the 1 in 1,000 solution is the most promising method of treating Stokes-Adams attacks, and should be tried in every case. I have certainly seen marked benefit in one case, but in another it had no effect.

An injection of 5 to 10 minims may promptly relieve a hypoglycæmic reaction after insulin, as it helps to turn the glycogen out of the liver, and into the blood as dextrose.

The limitations of adrenal therapy in Addison's disease have already been fully discussed (Chapter VI). It will be noted that the greatest successes which have been obtained with adrenalin are not so much examples of substitution therapy as instances of its emergency action.

**The Ovaries and Corpus Luteum.**

Now that Allen and Doisy have isolated an ovarian hormone, which is available for general use, we may expect to obtain more precise data as to the effects of ovarian medication. No doubt some of the discrepant results obtained in the past are due to ignorance of the inhibitory effects of the presence of a corpus luteum in the ovary employed in the preparation of the extract. Since the publication of Dixon and Marshall's observations greater care has been exercised in this respect. Ovarian extract given by the mouth appears to help the vasomotor and nervous disturbances of the climacteric, either when natural or when induced by operation, and in the irregular or delayed menstruation at puberty. I have also used it in female hypopituitarism, because of its known effect in stimulating the pituitary, as well as in cases of hypogonadal obesity. I have seen apparent benefit from it in rheumatoid arthritis, chiefly at the time of the climacteric. I was led to use it from Cumberbatch's observations on the value of diathermy to the cervix in rheumatoid arthritis, even when no infective

factor was found there. He suggested that this treatment probably stimulated the ovaries. It helped decidedly in a case of thymic asthma in a girl of 17, presumably by restoring the endocrine balance between the thymus and the gonads. Corpus luteum, on the other hand, by its inhibitory effect on the pituitary, has had a striking effect in checking pathologically prolonged lactation, and some effect on pituitary headaches. It also seems to have an influence in habitual abortion; in one case I saw its use promptly followed by successful pregnancy after six years of sterility. This is comprehensible since we know that destruction of the corpus luteum is inevitably followed by abortion. It has also been recommended for the nausea and vomiting of pregnancy.

**The Testes.**

I am doubtful as to the value of any orchitic extract given by the mouth. It has been recommended for delayed puberty, impotence and enlargement of the prostate. I have certainly seen puberty develop during its administration, but I cannot help thinking that this could have occurred without the drug. In one case of hypopituitarism with feminism, the administration of orchitic extract was followed by descent of the testis and a premature adolescence of a markedly virile type. I should be glad to think we possessed a preparation of such great potency, but I hesitate to ascribe the change to its use, since it was given between the age of 12 and 14, when puberty might normally have occurred, and the anterior lobe of the pituitary become more active. Still, since both experimental and surgical evidence point to the existence of an internal secretion by the testis, I believe that in the future definite results will be obtained, if only an active hormone comparable to the ovarian hormone of Allen and Doisy can be isolated.

**Other Glandular Extracts.**

I am sceptical as to the value of extracts of the thymus, pineal, prostate, placenta and mammary gland. At any rate, I have never seen any results which seemed to me could be ascribed with certainty to their administration,

though I am aware that this does not accord with the experience of others.

**Insulin.**

The use of insulin in diabetes lies outside my present topic. It is sufficient to record my profound conviction as to its great value, and my regret for the prejudice which has been deliberately excited against it in certain quarters. Those who circulate alarmist statements about insulin do great harm, and take a heavy responsibility upon themselves. Here I wish to refer to the use of the drug in other conditions. I believe it to be of great service in stabilising the weight and basal metabolism in hyperthyroidism. I would also advocate its use in the acute hyperthyroidism following operations on the gland. Cramer has shown that insulin can prevent death in the experimental hyperpyrexia produced by tetra-hydro-naphthylamine (T.H.N.), through its activating effect on the thyroid, pituitary and adrenals, to all of which glands insulin is antagonistic. There is therefore rational sanction for using the drug in clinical hyperpyrexia. I have used it repeatedly in combination with dextrose to check wasting in anorexia nervosa. First I inject 5 units of insulin shortly after the oral administration of 15 grammes of dextrose; if this is well borne I double the dose both of insulin and dextrose, giving them once daily. The insulin compels the assimilation of the sugar, and a slight but steady increase in weight can generally be secured. I have also employed the method with benefit in other forms of nervous wasting. Finally, I would warmly commend the combined use of insulin and dextrose in hepatic toxæmias, such as delayed anæsthetic poisoning, salvarsan or atophan poisoning, cyclical vomiting and the toxæmias of pregnancy. Dextrose has been used in such conditions for some years, but by giving insulin as well we can not only help the liver by increasing its glycogen reserves, but can also assist in the complete oxidation of the fats which are producing the toxic enolic bodies. Of late I have been using this method as a precautionary measure before operation in cases where a liability to acidæmia is suspected, or where post-operation shock is feared; the results are encouraging.

## CHAPTER XII

# THE FUTURE OF ENDOCRINOLOGY

To obtain a general conception of the principles of internal secretion it is necessary to start from the premise that the development of each individual recapitulates, briefly and with modifications, the history of the race. And it is helpful to remember that, while life has been present on the earth for millions of years, man did not appear more than a comparatively few thousand years ago. Every time an individual repeats the history of the race he does it more easily as the result of practice. Thus it happens that the fœtus in nine short months of pre-natal life recapitulates the history of millions of years, while his longer infantile life only repeats the history of a few thousand years.

Now the most primitive forms of life multiplied by simple fission. The unfertilised ovum is the nearest approach to the primordial cell that we know. Like the primordial cell it starts to divide by simple fission, forming two polar bodies. Millions of years ago simple fission was found inadequate for a complex animal, yet every ovum starts on this course till it is abruptly brought up by the consequent exhaustion of its powers of growth. But when fertilisation has re-made its nuclear network, a tremendous impetus is given to growth. The impetus thus derived gradually wears itself out. If growth is measured, not by total bulk, but by the percentage of the previous total added in a given time, it will be found that the growth of a child shows a continuous falling off. Minot has estimated that less than 2% of the total potentiality of growth resident in the human ovum is still present at birth.

A new life may be compared to a projectile travelling with a constantly diminishing velocity. But, unlike an

ordinary projectile, it is supplied with intrinsic regulators capable of increasing or diminishing that velocity. These regulators are the two groups of endocrine glands and their associated nervous mechanisms. In the first few years of life the original impetus is so enormous that a brake is needed—which seems to act chiefly through the thymus. By seven years of age this brake is needed no longer, and should it continue to be applied from any cause, infantile features persist. With the aid particularly of the thyroid and pituitary active growth continues, until puberty gives another twist to the mechanism from the active development of another set of glands ; a new position of equilibrium has to be found. With adult years a part of the energy is diverted from growth of the individual to providing a supply for the next generation ; and again the regulators have to provide a new adjustment. Another jolt—often a violent one—is given to the mechanism by the climacteric, and yet a new position of equilibrium has to be acquired. From this point on the dying down of the initial velocity is marked ; calcium fixation goes on unchecked, the intercostal carilages grow rigid, the chest becomes emphysematous, greatly diminishing the bodily activities by restricting the respiratory exchange, the arteries become calcareous, diminishing the blood flow to every part of the body, while childish and even infantile characters may reappear as the organism slows down for the terminus.

This may be considered the normal course of events. That everybody should ultimately only die from senile decay is the goal of medicine. But apart from violent death, the regulators may become worn out, with consequent great increase of friction to the mechanism. Invasion by bacteria and their toxins may prematurely exhaust the endocrine glands, or endogenous poisons may produce a similar effect ; metabolism becomes balanced on a razor edge, the sport of every wind that blows. Nervous shocks and strains excite a reaction of the sympathetic nervous system and, through it, of its associated chain of endocrine glands, with consequent exhaustion of them. And these two sources of endocrine exhaustion may interact, so that a psychic conflict may be produced because the body cannot adjust itself to a

difficult environment, largely because of an endocrine deficiency. Thus the two newest methods in medicine, psychotherapy and endocrinology, become not opposed, but different aspects of the same problem. Or a body may start out ill-equipped with a supply of endocrines, as in progeria and dementia præcox.

In amplifying this general conception of the action of the endocrine system clinical observation must continue to play a large part by the careful study of abnormal types, and correlating them with endocrine disturbances when present. The pioneer observations on the subject were made at the bed-side; the association of myxœdema and cretinism with the thyroid, of acromegaly and Fröhlich's syndrome with the pituitary and of Addison's disease with the adrenals, each of these was pointed out by clinicians before any laboratory observations had been made on the subject. There is no need, therefore, to apologise for using empirical methods. Empiricism has often won therapeutic success which had to wait long for scientific explanation—such as quinine for malaria, and mercury for syphilis; and which in some cases has not received it, such as salicylates for rheumatism and colchicum for gout. The empirical method has always been suspect by the laboratory, although it is a procedure by trial and error just as the experimental method is; I think I may add, unfairly suspect, when one remembers that cod-liver oil was used for many years, to the scorn of the experimentalist, until vitamins were discovered, and then he scoffed no more. But the lack of adequate controls from which clinical work must always suffer makes it doubly necessary to employ the empirical method in a critical spirit, realising its fallacies and checking it by laboratory methods whenever possible.

"Never prophesy unless you know" is a wise saying, and worthy of all acceptance. The way of prognosis is hard and beset with fallacies. Nevertheless, from a consideration of the present trend of endocrinology one can arrive at certain conclusions as to the probable future developments. I shall consider these under four heads.

(1) A study of definite endocrine diseases, such as

myxœdema, acromegaly and Addison's disease, was followed by a recognition of minor degrees of endocrine disturbances. It was soon noted that these were associated with certain psychological peculiarities. Then similar though less marked psychological traits were recognised in normal and slightly sub-normal individuals. They could not be regarded as cases of disease at all, but the study of disease had enabled them to be classed as of a certain endocrine pattern. The creative activity of the thyroid, the aggressive masculine drive of the adrenals, the rhythmical, musical, or mathematical characteristics of the individual with a well-developed pituitary became recognised. Such observations must ultimately have a profound influence in two directions, the study of the psycho-neuroses from a new angle, and an important part in determining a child's vocation. There will be much less fitting of square pegs into round holes when the doctor is able to offer advice based on scientific facts as to the endocrine and, therefore, as to the psychological make-up of the growing individual. It has always seemed to me probable that endocrine inheritance follows Mendelian laws, and I have been very interested to find that work which is now in progress along these lines is confirming that opinion. But although a family may have a tendency, for instance, to thyroid disease, there may be overaction of the gland in one member and underaction in another. So far we are ignorant of what determines the push in one direction or the other.

(2) The initial success won by thyroid treatment led to disappointment when it was found that a satisfactory substitution therapy was not nearly so easily obtained with other glands. The reasons for this difference have been already discussed. It was realised that there was no short cut to general success in organotherapy. The physiology of each gland had to be studied. Whenever the active principle of a gland has been isolated, therapeutical advance has speedily followed. Adrenalin and pituitrin were the first to be thus obtained, and it is only within the last few years that insulin, and the hormones of the parathyroid and ovary have been added to the list. It is curious that the discovery of the active principle

of the thyroid lagged so far behind the discovery of its secretion. Only within the last few months has its structural formula been agreed upon. It would seem as if the very ease with which the secretion could be employed discouraged research on this point. Where a gland had an obvious function, but failed therapeutically, there was a greater inducement to try and solve the problem. It can hardly be doubted that the isolation of the hormones of the anterior pituitary, of the adrenal cortex, and of the testes, will be achieved in the near future. Since the administration of endocrine preparations by the mouth is of comparatively limited application, a search is beginning for methods of influencing the endocrine glands by drugs. Here there is a wide field for the pharmacologist. It is, indeed, believed by some that the main effect of drugs on the body is through the chemical mechanisms situated in these glands. Yet so far we have hardly got beyond the use of iodine to influence the thyroid. Ergotamine has been used to some extent for its action in removing secretory and motor effects of the sympathetic nervous system, while leaving the inhibitory effect unimpaired. Considering the close association between the sympathetic and one group of endocrines this may have practical application in the future ; while the influence of acetyl-cholin on the parasympathetic may be utilised in the control of the opposing group. The physiological antagonisms between certain endocrines must almost certainly have a simple chemical explanation, and once this is grasped and understood the field for the pharmacological control of endocrine disturbances will be much extended.

(3) A study of such antagonisms and of the interactions of the endocrines between themselves will continue to give valuable results. When it is not possible to get an endocrine preparation absorbed, use may be made of such co-operation and antagonism. Examples of this have been given. It may be convenient to summarise in tabular form the influence of the sympathetic group of endocrines on various important bodily functions, so that these relationships may be seen at a glance.

| | *Sex.* | *Growth.* | *Glycosuria.* | *Vasomotor System.* |
|---|---|---|---|---|
| *Thyroid* .. | ♀ | + | + | Dilator |
| *Adrenal*— | | | | |
| Cortex .. | ♂ | + | ○ | ○ |
| Medulla .. | ○ | ○ | + | Constrictor |
| *Pituitary*— | | | | |
| Anterior .. | ♂ | + | ? | ○ |
| Posterior .. | ♀ | ○ | + | Constrictor |

The relationship of the parathyroid and the pancreatic cell islets cannot yet be expressed in the same concrete form, but it would be generally accepted that they co-operate between themselves and are broadly antagonistic to the above group. Recent work goes to show, for instance, how delicately the balance between insulin and the thyroid secretion is held, and what profound and even fatal disturbances may follow if it is upset.

(4) Finally, we have learnt more of the interactions between the endocrines and the liver; which opens out fresh methods of treatment in hepatic disease. The thyroid is a general quickener of metabolism, and the liver shares in this quickening. The bile flows more quickly and contains less bile salts. This is sometimes useful in the treatment of stagnant infected conditions of the gall-bladder. But as it also helps to empty the glycogen reservoirs, the method must be used with caution and controlled by administration of sugar. Adrenalin also diminishes the glycogen content of the liver, while increasing its content of fat. In both these respects it is antagonistic to insulin. Here pituitrin appears to act like adrenalin.

The liver plays an important part in fat metabolism. It takes saturated fat from the tissues and desaturates them, in which form they are ready for consumption. We may compare the liver to the miller, the saturated fats to the grain, and the unsaturated fats to flour. When the miller goes on strike, the tissues, which are starving for flour, keep on sending grain to the mill, where it is piled up. Now, recent work has shown that pituitrin is the great transporter of the grain to the mill. Thus we can

understand why the subject of hypopituitarism is obese ; and since the subject of gonadal deficiency fails to activate his pituitary, why he also is fat. When the liver is below par, it finds great difficulty in fat metabolism, while a copious supply of glycogen helps it to carry out simpler duties. In hepatic toxæmias, as has already been pointed out, dextrose has been found useful, and its usefulness will be increased by insulin, since this will, at the same time, aid the glycogenic function and help in the oxidation of fats, incomplete combustion of which leads to the formation of toxic acids. The use of insulin in addition to dextrose is to be advocated in hepatic toxæmias therefore, while it would appear that pituitrin and adrenalin are specially to be avoided.

Such may be taken merely as illustrations of the lines of work which appear to me to be of promise in developing the future of endocrinology. To sum them up : as the psychological make-up depends in large part on the endocrine pattern, endocrinology will play an increasing part in the study of the psycho-neuroses, and in the rational determination of vocation ; pharmacology will come to the aid of substitution therapy ; greater use will be made of the antagonisms and co-operations between the different endocrines ; and endocrinology will help in the treatment of hepatic diseases. Such surgical procedures as partial thyroidectomy and grafting operations lie outside my topic, but I may say that these are being and will be still more efficiently studied in the light of their effects on basal metabolism and carbohydrate tolerance.

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